

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



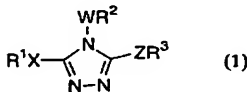
(43) International Publication Date
14 August 2003 (14.08.2003)

PCT

(10) International Publication Number
WO 03/065983 A2

- (51) International Patent Classification⁷: **A61K** 07065-0907 (US). **OLSON, Steven, H.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
(21) International Application Number: PCT/US03/02558 **MALETIC, Milana** [YU/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
(22) International Filing Date: 28 January 2003 (28.01.2003)
(25) Filing Language: English
(26) Publication Language: English
(30) Priority Data: 60/353,592 1 February 2002 (01.02.2002) US
(71) Applicant (for all designated States except US): **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
(72) Inventors; and
(75) Inventors/Applicants (for US only): **BALKOVEC, James, M.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **THIERINGER, Rolf** [DE/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **MUNDT, Steven, S.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **HERMANOWSKI-VOSATKA, Anne** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **GRAHAM, Donald, W.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **PATEL, Gool, F.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **ASTER, Susan, D.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **WADDELL, Sherman, T.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
Published:
— without international search report and to be republished upon receipt of that report
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 11-BETA-HYDROXYSTEROID DEHYDROGENASE 1 INHIBITORS USEFUL FOR THE TREATMENT OF DIABETES, OBESITY AND DYSLIPIDEMIA



(57) Abstract: Compounds having Formula (I), including pharmaceutically acceptable salts and prodrugs thereof: are selective inhibitors of the 11 β -HSD1 enzyme. They inhibit the 11 β -HSD1-mediated conversion of cortisone and other 11-keto-glucocorticoids to cortisol and other 11 β -hydroxy-glucocorticoids. The 11 β -HSD1 inhibitors therefore decrease the amount of cortisol in target tissues, thereby modulating the effects of cortisol. Modulation of cortisol may be effective in controlling non-insulin-dependent diabetes (NIDDM), hyperglycemia, obesity, insulin resistance, dyslipidemia, hyperlipidemia, hypertension, Syndrome X, and other symptoms associated with NIDDM or with excess cortisol in the body.

WO 03/065983 A2

Persistent or uncontrolled hyperglycemia that occurs with diabetes is associated with increased and premature morbidity and mortality. Often abnormal glucose homeostasis is associated both directly and indirectly with obesity, hypertension, and alterations of the lipid, lipoprotein and apolipoprotein metabolism and other metabolic and hemodynamic disease. Therefore patients with type 2 diabetes mellitus are at an especially increased risk of macrovascular and microvascular complications, including atherosclerosis, coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. Therefore, therapeutic control of glucose homeostasis, lipid metabolism, obesity, and hypertension are critically important in the clinical management and treatment of diabetes mellitus.

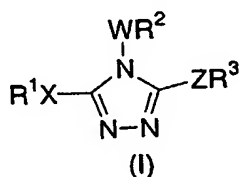
Many patients who have insulin resistance but have not developed type 2 diabetes are at a risk of developing at least several symptoms selected from a group of symptoms that are often referred to as syndrome X, or the metabolic syndrome. This syndrome is characterized by insulin resistance, abdominal obesity, hyperinsulinemia, high blood pressure, low HDL, and high VLDL. These patients, whether or not they develop overt diabetes mellitus, are at increased risk of the macrovascular and microvascular complications of type 2 diabetes listed above (e.g. atherosclerosis and coronary heart disease).

Insulin resistance is not primarily due to a diminished number of insulin receptors but to a post-insulin receptor binding defect that is not yet completely understood. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in the liver.

The available treatments for type 2 diabetes have not changed substantially in many years, and these treatments have recognized limitations. Physical exercise and reductions in dietary intake of calories often dramatically improve the diabetic condition, but compliance with this treatment is very poor because of well-entrenched sedentary lifestyles and excess food consumption, especially of foods containing high amounts of saturated fat. Increasing the plasma level of insulin by administration of sulfonylureas (e.g. tolbutamide and glipizide) or meglitinide, which stimulate the pancreatic β -cells to secrete more insulin, and/or by injection of insulin when sulfonylureas or meglitinide become ineffective, can result in insulin concentrations high enough to stimulate the very insulin-resistant tissues.

- 5 cortisol and other 11 β -hydroxysteroids in target tissues, thereby reducing the effects of excessive amounts of cortisol and other 11 β -hydroxysteroids. Inhibition of 11 β -HSD1 can be used to treat and control diseases mediated by abnormally high levels of cortisol and other 11 β -hydroxysteroids, such as NIDDM, obesity, hypertension, and dyslipidemia.

The compounds of the present invention have the structure shown in formula I below, or a pharmaceutically acceptable salt or prodrug thereof:

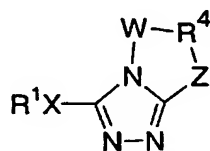


- In formula I:
- 10 R¹ is adamantyl, unsubstituted or substituted with one to five substituents independently selected from halogen, OCH₃, OCF₃, CH₃, CF₃, and phenyl, wherein said phenyl is unsubstituted or substituted with one to three halogens;
- 15 W is selected from the group consisting of NR^a and a single bond;
 X is selected from the group consisting of CH₂ and a single bond;
 Z is selected from the group consisting of S and a single bond;
- R^a is selected from the group consisting of hydrogen and C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five fluorines;
- 20 R² is selected from the group consisting of
 hydrogen,
 C₁₋₁₀ alkyl, unsubstituted or substituted with one to six substituents
 independently selected from zero to five halogens and zero or one group selected from
 25 hydroxy and C₁₋₃ alkoxy, said alkoxy group being unsubstituted or substituted with
 one to three halogens,
 C₂₋₁₀ alkenyl, unsubstituted or substituted with one to six substituents
 independently selected from zero to five halogens and zero or one group selected from
 hydroxy and C₁₋₃ alkoxy, said alkoxy group being unsubstituted or substituted with
 30 one to three halogens,

R is selected from the group consisting of benzodioxolane, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, dihydropyran, tetrahydropyran, pyridine, piperidine, benzofuran, dihydrobenzofuran, benzothiophene, dihydrobenzothiophene, indole, dihydroindole, indene, indane, 1,3-dioxolane, 1,3-dioxane, phenyl, and naphthyl;
 5 wherein R is unsubstituted or substituted with one to four groups independently selected from halogen, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₂₋₄ alkenylsulfonyl, CN, OH, OCH₃, OCF₃, and C₁₋₄ alkyl, said C₁₋₄ alkyl being unsubstituted or substituted with one to five halogens or one substituent selected from
 10 OH and C₁₋₃ alkoxy; and

Y is selected from (CH₂)₀₋₂ and (-HC=CH-);

or alternatively R² and R³ taken together form a bridging group R⁴, providing a
 15 compound of structural formula Ia:



Ia

wherein R⁴ is

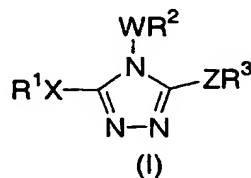
a C₂₋₈ alkylene group, optionally containing one heteroatom selected from O
 20 and NR^b between two adjacent carbon atoms of said C₂₋₈ alkylene group, optionally containing one to two carbon-carbon double bonds when R⁴ is a C₃₋₈ alkylene group, and optionally also comprising a carbon-carbon single bond connecting two non-adjacent carbon atoms of said C₂₋₈ alkylene group, or

a C₄₋₈ cycloalkyl group;

25 wherein R^b is selected from the group consisting of hydrogen and C₁₋₆ alkyl, unsubstituted or substituted with one to six substituents independently selected from zero to five fluorines and zero or one phenyl, said phenyl being unsubstituted or substituted with one to three substituents independently selected from halogen, CH₃, CF₃, OCH₃, and OCF₃;

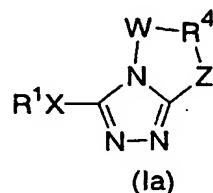
DETAILED DESCRIPTION OF THE INVENTION

The compounds of structural formula I of the present invention have numerous embodiments, which are described below.



5

One embodiment comprises compounds having formula I as described above, where R^2 and R^3 are substituent groups but are not taken together to form a bridging group R^4 to provide a compound having formula Ia,



10

Another embodiment comprises compounds all of which have formula Ia as described above, but does not include compounds that have formula I.

Another embodiment comprises compounds having formula I as described above, wherein

15 R^1 is adamantyl, unsubstituted or substituted with one to five substituents independently selected from halogen, OCH_3 , OCF_3 , CH_3 , CF_3 , and phenyl, wherein said phenyl is unsubstituted or substituted with one to three halogens;

X , W , and Z are single bonds;

20 R^2 is selected from the group consisting of

hydrogen,

C_{1-6} alkyl, unsubstituted or substituted with one to four substituents

thiophene, dihydrobenzofuran, tetrahydrofuran, tetrahydropyran, and indane, wherein R is unsubstituted or substituted with one to three halogens.

Another embodiment of compounds of the present invention comprises compounds that have formula I but not formula Ia as described above, wherein

- 5 R¹ is adamantyl, unsubstituted or substituted with one to five substituents independently selected from halogen, OCH₃, OCF₃, CH₃, CF₃, and phenyl, wherein said phenyl is unsubstituted or substituted with one to three halogens;

X is a single bond;

- 10 Z is S;

WR² is selected from the group consisting of

- NH₂,
hydrogen,
15 C₁₋₆ alkyl, unsubstituted or substituted with one to four substituents independently selected from zero to three halogens and zero or one group selected from hydroxy and methoxy,
C₂₋₄ alkenyl, unsubstituted or substituted with one to three halogens,
(CH₂)₀₋₁C₃₋₆ cycloalkyl, and
20 (CH₂)₀₋₂R, wherein R is selected from the group consisting of phenyl, furan, tetrahydrofuran, and piperidine; wherein R and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from halogen, OCH₃, OCF₃, CH₃, and CF₃; and

- 25 R³ is selected from the group consisting of
hydrogen,
C₁₋₆ alkyl, unsubstituted or substituted with hydroxy, methoxy, or one to five halogens,
C₂₋₆ alkenyl, unsubstituted or substituted with hydroxy, methoxy, or one to
30 five halogens,
(CH₂)₀₋₂C₃₋₈ cycloalkyl, wherein cycloalkyl has one double bond and is unsubstituted or substituted with one to four substituents independently selected from the group consisting of (a) zero to three halogens and methyl and (b) zero or 1 phenyl, and

zero to five fluorines and zero to one phenyl, said phenyl being unsubstituted or substituted with one to three substituents independently selected from halogen, CH₃, CF₃, OCH₃, and OCF₃;

5 wherein R⁴ is unsubstituted or substituted with one to five R^C substituents, wherein each R^C is independently selected from halogen, OH, OCH₃, OCF₃, C₁₋₆ alkyl, C₂₋₆ alkenyl, phenyl, biphenyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyloxycarbonyl, an epoxide group bridging 2 adjacent carbons, and 1,3-dioxolanyl geminally disubstituted onto one carbon of R⁴, wherein each C₁₋₆ alkyl and C₂₋₆ alkenyl is unsubstituted or
10 substituted with one to five substituents independently selected from zero to three halogens and zero to two groups selected from phenyl, C₁₋₆ alkyloxycarbonyl, 1,3-dioxolanyl geminally disubstituted onto one carbon, and CN, and wherein each phenyl, biphenyl, and C₃₋₈ cycloalkyl, either as R^C or as a substituent on R^C, is unsubstituted or substituted with one to three groups independently selected from
15 halogen, CH₃, CF₃, OCH₃, and OCF₃;

15 wherein R⁴ optionally has a fused phenyl ring, a benzodioxinyl ring, or a dihydrobenzodioxinyl ring, said phenyl ring, benzodioxinyl ring, and dihydrobenzodioxinyl ring being unsubstituted or substituted with one to three substituents independently selected from halogen, CH₃, CF₃, OCH₃, and OCF₃; and

20 wherein R⁴, including said optional fused phenyl ring, benzodioxinyl ring, or dihydrobenzodioxinyl ring and including all substituents on R⁴ and said fused phenyl ring, benzodioxinyl ring, or dihydrobenzodioxinyl ring, has no more than 20 carbon atoms.

25 Another embodiment of compounds having formula I or formula Ia as described above, comprises compounds in which Z is S and WR² is selected from NH₂ and R².

Another subset of compound having formula I or formula Ia as described above includes compound in which W and Z are single bonds.

30 Illustrative, but nonlimiting, examples of compounds of the present invention that are useful as inhibitors of the 11-beta-hydroxysteroid dehydrogenase Type I enzyme are the following:

include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, and the like.

"Alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof, unless the carbon chain is defined otherwise. Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

"Alkynyl" means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

"Alkylene" refers to carbon chains that are bifunctional, such as -CH₂-, -(CH₂)₂-, -(CH₂)₃-, and the like. Alkylene groups are linear or branched, unless otherwise indicated. For comparison, alkyl groups are monofunctional.

"Cycloalkyl" means a saturated carbocyclic ring having a specified number of carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like. A cycloalkyl group generally is monocyclic unless stated otherwise. Bicycloalkyl and tricycloalkyl are bicyclic and tricyclic carbocyclic ring systems. Cycloalkyl, bicycloalkyl and tricycloalkyl groups are saturated unless otherwise defined.

"Aryl" means a mono- or polycyclic aromatic ring system containing only carbon ring atoms. The preferred aryls are monocyclic or bicyclic 6-10 membered aromatic ring systems. Phenyl and naphthyl are preferred aryls. The most preferred aryl is phenyl.

"Heterocycle" means a saturated or unsaturated ring (including aromatic rings) containing at least one heteroatom selected from N, S and O (including SO and SO₂). Examples of heterocycles include tetrahydrofuran, piperidine, piperazine, morpholine, thiomorpholine, and tetrahydrothiophene 1,1-dioxide.

"Heteroaryl" means an aromatic heterocycle that contains at least one ring heteroatom selected from N, O and S (including SO and SO₂). Heteroaryls can be fused to other heteroaryls or to other kinds of rings, such as aryls, cycloalkyls and heterocycles that are not aromatic. Examples of monocyclic heteroaryl substituents include pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, and

If desired, racemic mixtures of compounds of Formula I and Formula Ia may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds of Formula I or Formula Ia to an enantiomerically pure
5 compound to form a diastereomeric mixture, which is then separated into individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to the pure enantiomers by cleaving the added chiral residue from the
10 diastereomeric compound. The racemic mixture of the compounds of Formula I or Formula Ia can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

Alternatively, enantiomers of compounds of the general Formula I and Formula Ia may be obtained by stereoselective synthesis using optically pure starting
15 materials or reagents of known configuration. Such methods are well known in the art.

Compounds of Formula I and Ia may have more than one asymmetric center. Such compounds may occur as mixtures of diastereomers, which can be separated into individual diastereomers by standard methods, and the diastereomers can
20 be further separated to individual enantiomers as described above.

Salts:

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or
25 organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the
30 form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-
35 dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-

Biochemical Mechanism:

The compounds of this invention are selective inhibitors of the 11 β -HSD1 enzyme. Their utility in treating type 2 diabetes, high blood pressure, dyslipidemia, obesity, and other diseases and conditions is believed to derive from the biochemical mechanism described below. This mechanism is provided for clarification only, and is non-limiting as to the scope and utility of the compounds claimed.

Corticosteroids, also referred to as glucocorticoids, are steroid hormones that play an important physiological role in mammals, including humans. Control (also referred to as modulation) of glucocorticoid activity is important in regulating physiological processes in a wide range of tissues and organs.

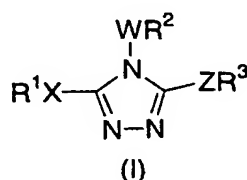
Glucocorticoid concentrations are modulated by the tissue-specific 11 β -hydroxysteroid dehydrogenase enzymes. The two enzymes (also referred to as isozymes) of 11 β -HSD (11 β -HSD1 and 11 β -HSD2) have different cofactor requirements and substrate affinities (See Figure 1). Each has been successfully cloned in both rat and human tissues. The 11 β -hydroxysteroid dehydrogenase type 2 enzyme (11 β -HSD2) is a high affinity enzyme (K_m for glucocorticoid = 10 nM) that generally uses NAD⁺ as the preferred cofactor and rapidly dehydrogenates 11 β -hydroxy-glucocorticoids, such as cortisol, to 11-keto glucocorticoids, such as cortisone. The 11 β -hydroxysteroid dehydrogenase type 1 enzyme (11 β -HSD1) is a low affinity enzyme that generally uses NADP⁺ as a cofactor rather than NAD⁺ (Agarwal *et al.*, 1994, *J. Biol. Chem.*, 269: 25959-25962). *In vitro* studies have shown that 11 β -HSD1 is capable of acting as both a reductase and a dehydrogenase. However, 11 β -HSD1 *in vivo* generally acts as a reductase, converting 11-ketoglucocorticoids, such as cortisone, to 11 β -hydroxyglucocorticoids such as cortisol.

conversion of cortisol to cortisone, so that the amount of cortisol available for binding to the mineralocorticoid receptor increases, resulting in hypertension.

The activity of 11 β -HSD2 is also high in the placenta. This may protect the fetus from elevated levels of circulating cortisol, which may be detrimental to the health of a developing fetus.

Utilities:

The present invention also relates to the use of a compound of structural formula I or Ia



wherein:

R¹ is adamantyl, unsubstituted or substituted with one to five substituents independently selected from halogen, OCH₃, OCF₃, CH₃, CF₃, and phenyl, wherein said phenyl is unsubstituted or substituted with one to three halogens;

W is selected from the group consisting of NR^a and a single bond;

X is selected from the group consisting of CH₂ and a single bond;

Z is selected from the group consisting of S and a single bond;

R^a is selected from the group consisting of hydrogen and C₁-6 alkyl, wherein alkyl is unsubstituted or substituted with one to five fluorines;

R² is selected from the group consisting of

hydrogen,

C₁-10 alkyl, unsubstituted or substituted with one to six substituents

independently selected from zero to five halogens and zero or one group selected from hydroxy and C₁-3 alkoxy, said alkoxy group being unsubstituted or substituted with one to three halogens,

unsubstituted or substituted with one to six substituents independently selected from (a) zero to five halogens, CH₃, CF₃, OCH₃, and OCF₃, and (b) zero or one phenyl, said phenyl being unsubstituted or substituted with one to four groups independently selected from halogen, OCH₃, OCF₃, CH₃, and CF₃;

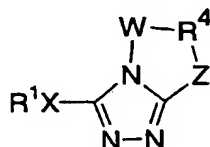
5

R is selected from the group consisting of benzodioxolane, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, dihydropyran, tetrahydropyran, pyridine, piperidine, benzofuran, dihydrobenzofuran, benzothiophene, dihydrobenzothiophene, indole, dihydroindole, indene, indane, 1,3-dioxolane, 1,3-dioxane, phenyl, and naphthyl; wherein R is unsubstituted or substituted with one to four groups independently selected from halogen, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₂₋₄ alkenylsulfonyl, CN, OH, OCH₃, OCF₃, and C₁₋₄ alkyl, said C₁₋₄ alkyl being unsubstituted or substituted with one to five halogens or one substituent selected from OH and C₁₋₃ alkoxy; and

15

Y is selected from (CH₂)₀₋₂ and (-HC=CH-);

or alternatively R² and R³ taken together form a bridging group R⁴, providing a compound of structural formula Ia:



20

Ia

wherein R⁴ is

a C₂₋₈ alkylene group, optionally containing one heteroatom selected from O and NR^b between two adjacent carbon atoms of said C₂₋₈ alkylene group, optionally containing one to two carbon-carbon double bonds when R⁴ is a C₃₋₈ alkylene group, and optionally also comprising a carbon-carbon single bond connecting two non-adjacent carbon atoms of said C₂₋₈ alkylene group, or

25

a C₄₋₈ cycloalkyl group;

wherein R^b is selected from the group consisting of hydrogen and C₁₋₆ alkyl,

30

unsubstituted or substituted with one to six substituents independently selected from

contribute to the symptoms of these diseases and conditions if it is present in excessive amounts.

NIDDM, Hypertension. In a second aspect, the compounds of this invention are selective for inhibition of 11β -HSD1 in comparison with 11β -HSD2. 5 Inhibition of 11β -HSD2 can cause serious side effects, such as hypertension. It was previously demonstrated that 11β -HSD1 inhibitors can ameliorate some of the symptoms of NIDDM, such as insulin resistance (B. R. Walker et al., 1995, J. Clin. Endocrinol. Metab., 80: 3155-3159). However, these studies were carried out using glycyrrhetic acid and carbenoxolone, which are inhibitors of both 11β -HSD1 and 10 11β -HSD2. Glycyrrhetic acid and carbenoxolone are believed to cause hypertension through the inhibition of 11β -HSD2.

Cortisol is an important and well recognized anti-inflammatory agent. However, cortisol also has detrimental effects if present in large amounts. For example, cortisol acts as an antagonist to the action of insulin in the liver, so that 15 insulin sensitivity is reduced in the liver, resulting in increased gluconeogenesis and elevated levels of glucose in the liver. Therefore, patients who already have impaired glucose tolerance have a greater probability of developing type 2 diabetes in the presence of abnormally high levels of cortisol.

High levels of cortisol in tissues where the mineralocorticoid receptor 20 is present can lead to hypertension, as discussed in the previous section. The 11β -HSD2 enzyme effects the oxidation of cortisol to cortisone. The 11β -HSD1 enzyme acts as a reductase, converting cortisone to cortisol. It has been hypothesized that inhibition of 11β -HSD1 activity will shift the ratio of cortisol and cortisone in specific tissues toward a higher amount of cortisone, which is generally inactive, and a 25 reduced amount of cortisol, which is active and is often the cause of the symptoms. To the extent that elevated cortisol levels can lead to symptoms of Type 2 diabetes, inhibition of the activity of the 11β -HSD1 isozyme should modulate and control the symptoms of type II diabetes. Administration of a therapeutically effective amount of an 11β -HSD1 inhibitor therefore should be effective in treating, controlling, and 30 ameliorating the symptoms NIDDM, and administration of a therapeutically effective amount of an 11β -HSD1 inhibitor on a regular basis may actually delay or prevent the onset of Type II diabetes in a mammalian patient in need thereof, and particularly in a human patient.

Cushing's Syndrome. The effect of elevated levels of cortisol is also 35 observed in patients who have Cushing's syndrome, which is a metabolic disease

Therefore, administration of an effective amount of an 11β -HSD1 inhibitor may result in the reduction, amelioration, control or prevention of cognitive impairment associated with aging and of neuronal dysfunction

Atherosclerosis. As described above, inhibition of 11β -HSD1 activity and a reduction in the amount of cortisol can also be beneficial in treating or controlling hypertension, which otherwise can result from uncontrolled levels of cortisol. Since hypertension and dyslipidemia contribute to the development of atherosclerosis, administration of a therapeutically effective amount of an 11β -HSD1 inhibitor of this invention may be especially beneficial in treating, controlling, delaying the onset of, or preventing atherosclerosis.

Effects on Pancreas. Inhibition of 11β -HSD1 activity in isolated murine pancreatic β -cells improves glucose stimulated insulin secretion (B. Davani et al., J. Biol. Chem., 2000, 275: 34841-34844). Glucocorticoids were previously shown to reduce insulin secretion *in vivo*. (B. Billaudel et al., Horm. Metab. Res., 1979, 11: 555-560).

Reduction of Intraocular Pressure. Recent data suggests a connection between the levels of glucocorticoid target receptors and the 11β -HSD enzymes and the susceptibility to glaucoma (J. Stokes et al., Invest. Ophthalmol., 2000, 41: 1629-1638). Therefore, inhibition of 11β -HSD1 activity may be useful in reducing intraocular pressure in the treatment of glaucoma.

Immunomodulation. In certain disease states, such as tuberculosis, psoriasis, and stress in general, high glucocorticoid activity shifts the immune response to a humoral response, when in fact a cell based response may be more beneficial to the patient. Inhibition of 11β -HSD1 activity may reduce glucocorticoid levels, such as cortisol, thereby shifting the immune response to a cell based response. See D. Mason, Immunology Today, 1991, 12: 57-60, and G.A.W. Rook, Baillière's Clin, Endocrinol. Metab., 1999, 13: 576-581.

Osteoporosis. Glucocorticoids can inhibit bone formation, which can result in a net bone loss. Other data suggest that 11β -HSD1 may have a role in bone resorption. It therefore appears that inhibition of 11β -HSD1 may be beneficial in preventing bone loss due to osteoporosis. See C.H. Kim et al., J. Endocrinol., 1999, 162: 371-379; C.G. Bellows et al., Bone, 1998, 23: 119-125; and M.S. Cooper et al., Bone, 2000, 27: 375-381.

The above utilities are all believed to be achieved by treatment with 11β -HSD1 inhibitors. Since concurrent inhibition of 11β -HSD2 may have deleterious

Examples of other active ingredients that may be administered in combination with a compound of structural formula I, and either administered separately or in the same pharmaceutical composition, include, but are not limited to:

- (a) dipeptidyl peptidase IV (DP-IV) inhibitors;
- 5 (b) insulin sensitizers including (i) PPAR γ agonists such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, rosiglitazone, and the like) and other PPAR ligands, including PPAR α/γ dual agonists, such as KRP-297, and PPAR α agonists such as gemfibrozil, clofibrate, fenofibrate and bezafibrate, and (ii) biguanides, such as metformin and phenformin;
- 10 (c) insulin or insulin mimetics;
- (d) sulfonylureas and other insulin secretagogues such as tolbutamide, glipizide, meglitinide and related materials;
- (e) α -glucosidase inhibitors (such as acarbose);
- (f) glucagon receptor antagonists such as those disclosed in WO
15 98/04528, WO 99/01423, WO 00/39088 and WO 00/69810;
- (g) GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists such as those disclosed in WO00/42026 and WO00/59887;
- (h) GIP, GIP mimetics such as those disclosed in WO00/58360, and GIP receptor agonists;
- 20 (i) PACAP, PACAP mimetics, and PACAP receptor 3 agonists such as those disclosed in WO 01/23420;
- (j) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, cerivastatin, fluvastatin, atorvastatin, itavastatin, rosuvastatin, and other statins), (ii) bile-acid sequestrants (cholestyramine,
25 colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) nicotinyl alcohol, nicotinic acid or a salt thereof, (iv) inhibitors of cholesterol absorption, such as, for example, ezetimibe and beta-sitosterol, (v) acyl CoA:cholesterol acyltransferase inhibitors, such as, for example, avasimibe, and (vi) anti-oxidants, such as probucol;
- 30 (k) PPAR δ agonists, such as those disclosed in WO97/28149;
- (l) antiobesity compounds such as fenfluramine, dexfenfluramine, phentermine, sibutramine, orlistat, neuropeptide Y Y5 antagonists, CB1 receptor inverse agonists and antagonists, β 3 adrenergic receptor agonists, and melanocortin-receptor agonists, in particular melanocortin-4 receptor agonists;
- 35 (m) an ileal bile acid transporter inhibitor;

acceptable salt or prodrug thereof as an active ingredient, and a pharmaceutically acceptable carrier. Optionally other therapeutic ingredients may be included in the pharmaceutical compositions as discussed previously. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic
5 bases or acids, including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and
10 severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to
15 conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents
20 and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid
25 preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations should
30 contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered as intranasal
35 formulations, such as, for example, liquid drops or spray.

Percent inhibition was calculated relative to a non-inhibited control well and IC₅₀ curves were generated. This assay was similarly applied to 11 β -HSD2, whereby tritiated cortisol and NAD were used as the substrate and cofactor, respectively. To begin the assay, 40 μ L of substrate (25 nM ³H-Cortisone + 1.25 mM NADPH in 50 mM HEPES Buffer, pH 7.4) was added to designated wells on a 96-well plate. Solid compound was dissolved in DMSO at 10 mM followed by a subsequent 50-fold dilution in DMSO. The diluted material was then titrated 4 fold, seven times. 1 μ L of each titrated compound was then added in duplicate to the substrate. To start the reaction, 10 μ L of 11 β -HSD1 microsome from CHO transfectants was added to each well at the appropriate concentration to yield approximately 10% conversion of the starting material. For ultimate calculation of percent inhibition, a series of wells were added that represented the assay minimum and maximum: one set that contained substrate without compound or enzyme (background), and another set that contained substrate and enzyme without any compound (maximum signal). The plates were spun briefly at a low speed in a centrifuge to pool the reagents, sealed with an adhesive strip, mixed gently, and incubated at 37°C for 2 h. After incubation, 45 μ L of SPA beads, pre-suspended with anti-cortisol monoclonal antibody and non-specific 11 β -HSD inhibitor, were added to each well. The plates were resealed and shaken gently for greater than 1.5 h at 15°C. Data were collected on a plate based liquid scintillation counter such as a Topcount. To control for inhibition of anti-cortisol antibody/cortisol binding, substrate spiked with 1.25 nM ³H cortisol was added to designated single wells. 1 μ L of 200 μ M compound was added to each of these wells, along with 10 μ L of buffer instead of enzyme. Any calculated inhibition was due to compound interfering with the cortisol binding to the antibody on the SPA beads.

ASSAYS: MEASUREMENT OF IN VIVO INHIBITION

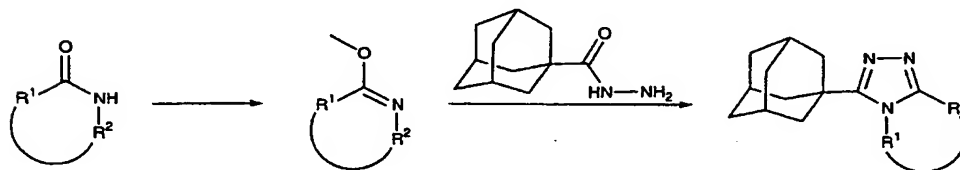
In general terms, a test compound was dosed orally to a mammal and a prescribed time interval was allowed to elapse, usually between 1 and 24 hours. Tritiated cortisone was injected intravenously, followed several minutes later by blood collection. Steroids were extracted from the separated serum and analyzed by HPLC. The relative levels of ³H-cortisone and its reduction product, ³H-cortisol, were determined for compound and vehicle-dosed control groups. The absolute conversion, as well as percentage of inhibition, was calculated from these values.

suspensions were prepared daily. Plasma glucose and triglyceride concentrations were determined from blood obtained by tail bleeds at 3-5 day intervals during the study period. Glucose and triglyceride, determinations were performed on a Boehringer Mannheim Hitachi 911 automatic analyzer (Boehringer Mannheim, Indianapolis, IN) using heparinized plasma diluted 1:6 (v/v) with normal saline. Lean animals were age-matched heterozygous mice maintained in the same manner.

The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

EXAMPLE 1

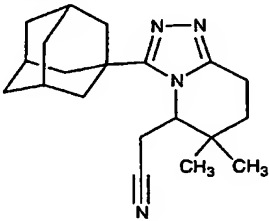
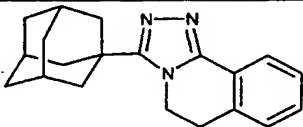
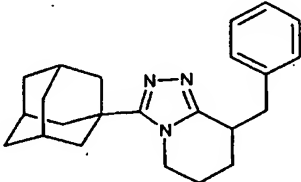
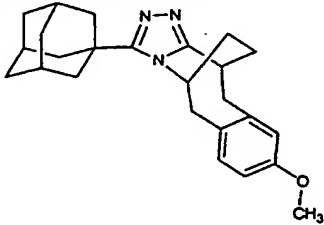
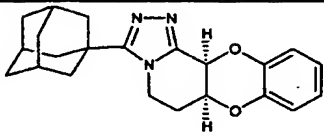
Scheme 1

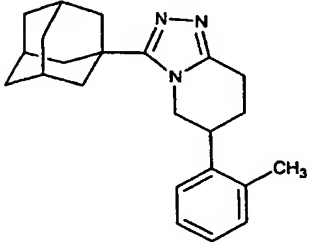
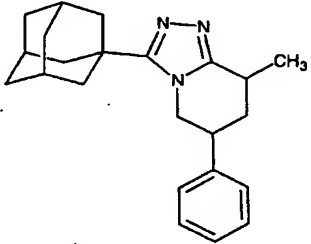
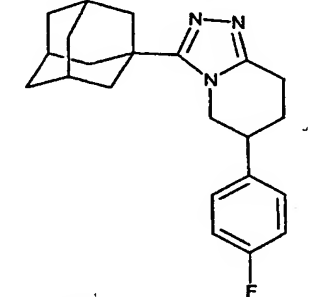
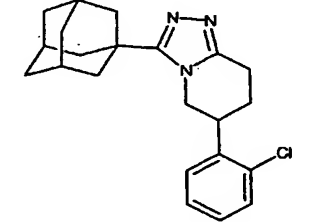
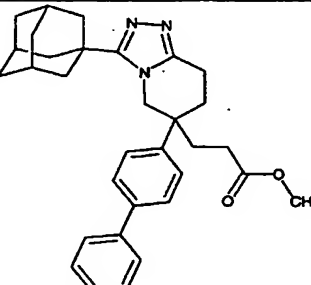


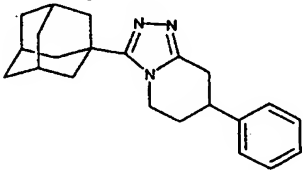
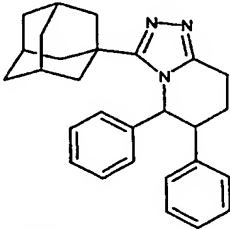
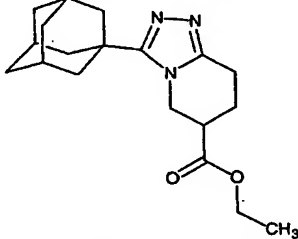
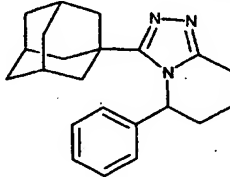
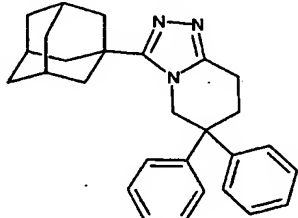
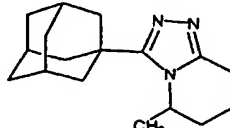
Procedure:

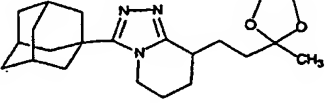
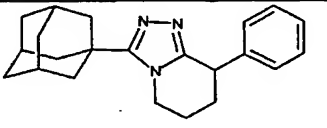
The following compounds were made as part of a one dimensional, single pure compound library on a Myriad Core System. All reaction vessels were dried under a stream of nitrogen at 120 °C for 12 h prior to use. All solvents were dried over sieves for at least 12 h prior to use. All subunits were dissolved in appropriate solvents immediately prior to use.

To each of the reaction vessels was added a methylene chloride solution of the X-component lactams (1.0 mL, 0.10 mmol, 0.1 M in methylene chloride). Next, was added a solution of triethyloxonium tetrafluoroborate (0.120 mL, 0.12 mmol, 1.0 M in methylene chloride). The reactions were aged for 20 h at room temperature. Then a solution of 2,6-di-tert-butyl-4-methylpyridine (0.240 mL, 0.12 mmol, 0.5M in methylene chloride) was added to each vessel. Then the methylene chloride was removed from the reactions via gas agitation. 2 mL of Anhydrous toluene was added to each vessel. Next, a solution of adamantyl hydrazide (1.0 mL,

<u>Ex.</u>	<u>Structure</u>	<u>Name</u>	<u>Retention Time (min)</u>	<u>MS ESI (m/z)</u>
<u>1-1</u>		3-(1-adamantyl)-5-(cyanomethyl)-6,6-dimethyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine trifluoroacetate salt	1.603	325.3
<u>1-2</u>		3-(1-adamantyl)-5,6-dihydro[1,2,4]triazolo[3,4-a]isoquinoline trifluoroacetate salt	1.663	306.1
<u>1-3</u>		3-(1-adamantyl)-8-benzyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine trifluoroacetate salt	1.807	348.03
<u>1-4</u>		3-(1-adamantyl)-9-methoxy-5,6,11,12-tetrahydro-5,12-ethano[1,2,4]triazolo[4,3-c][3]benzazocine trifluoroacetate salt	1.838	390.5
<u>1-5</u>		(+/-)-(6aRS,12aSR)-3-(1-adamantyl)-5,6,6a,12a-tetrahydro[1,4]benzodioxino[2,3-b]pyridine trifluoroacetate salt	1.782	363.9

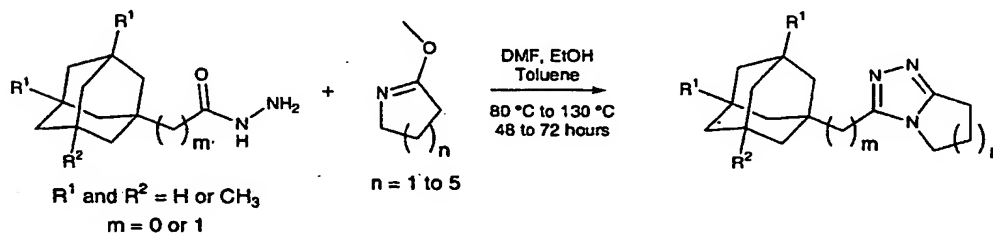
<u>1-10</u>		3-(1-adamantyl)-6-(2-methylphenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine trifluoroacetate salt	1.977	348.04
<u>1-11</u>		3-(1-adamantyl)-8-methyl-6-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine trifluoroacetate salt	1.963	348.3
<u>1-12</u>		3-(1-adamantyl)-6-(4-fluorophenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine trifluoroacetate salt	1.903	352.3
<u>1-13</u>		3-(1-adamantyl)-6-(2-chlorophenyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine trifluoroacetate salt	1.985	367.3
<u>1-14</u>		3-(1-adamantyl)-6-(1,1'-biphenyl-4-yl)-6-(3-methoxy-3-oxopropyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine trifluoroacetate salt	2.205	496.4

<u>1-19</u>		3-(1-adamantyl)-7-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine trifluoroacetate salt	1.812	334.2
<u>1-20</u>		3-(1-adamantyl)-5,6-diphenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine trifluoroacetate salt	2.187	410.5
<u>1-21</u>		3-(1-adamantyl)-6-(ethoxycarbonyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine trifluoroacetate salt	1.610	330.2
<u>1-22</u>		3-(1-adamantyl)-5-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine trifluoroacetate salt	1.857	334.0
<u>1-23</u>		3-(1-adamantyl)-6,6-diphenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine trifluoroacetate salt	2.123	409.8
<u>1-24</u>		3-(1-adamantyl)-5-methyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine trifluoroacetate salt	1.531	272.1

<u>1-30</u>		3-(1-adamantyl)-8-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine trifluoroacetate salt	2.361	394.5
<u>1-31</u>		3-(1-adamantyl)-8-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine trifluoroacetate salt	1.741	334.1

EXAMPLE 2**Scheme 2**

5

**Procedure:**

The following compounds were synthesized as part of a 2-D, single, pure compound library using a Myriad Core System. All reaction vessels were dried under a stream of nitrogen at 120 °C for 12 h prior to use. All solvents were dried over sieves for at least 12 h prior to use. All subunits (imino ethers and acyl hydrazides) were dissolved in appropriate solvents immediately prior to use. The following table details the amounts of the subunits and solvents used in the preparation of the library:

HPLC Purification Conditions:

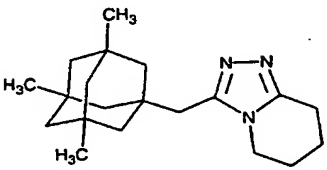
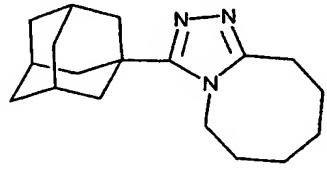
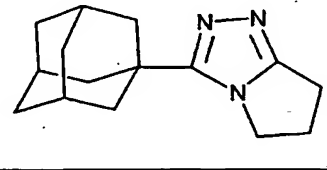
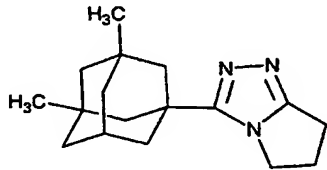
Analytical LC Method 1:

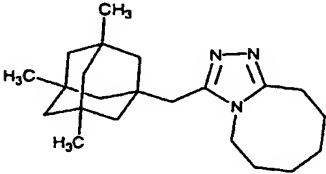
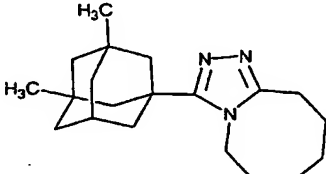
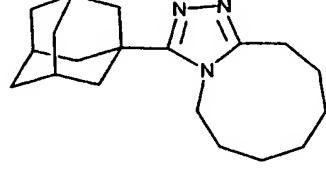
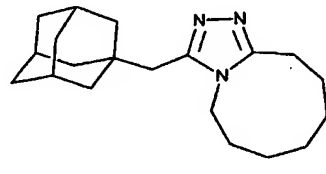
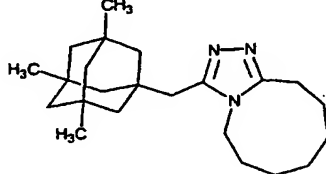
5	Column:	MetaChem Polaris C-18A, 30 mm X 4.6 mm, 5.0 µm
	Eluent A:	0.1% TFA in Water
	Eluent B:	0.1 % TFA in Acetonitrile
	Gradient:	5 % B to 95 % B in 3.3 min, ramp back to 5 % B in 0.3 min
10	Flow:	2.5 mL/min
	Column Temperature:	50 °C
	Injection amount:	5 µl of undiluted crude reaction mixture.
	Detection:	UV at 220 and 254 nm.
15		MS: API-ES ionization mode, mass scan range (100-600)
		ELSD: Light Scattering Detector

Preparative LC Method 2:

20	Column:	MetaChem Polaris C-18A, 100 mm X 21.2 mm, 10 µm
	Eluent A:	0.1% TFA in Water
	Eluent B:	0.1 % TFA in Acetonitrile
	Pre-inject Equilibration:	1.0 min
25	Post-Inject Hold:	1.0 min
	Gradient:	10 % B to 100 % B in 6.0 min, hold at 100 % B for an additional 2.0 min, ramp back from 100% B o 10 % B in 1.5 min
	Flow:	20 mL/min
30	Column Temperature:	ambient
	Injection amount:	1.5 mL of undiluted crude reaction mixture.
	Detection:	MS: API-ES ionization mode, mass scan range (100-600), fraction collection triggered by detection of M+1

Table of Compounds:

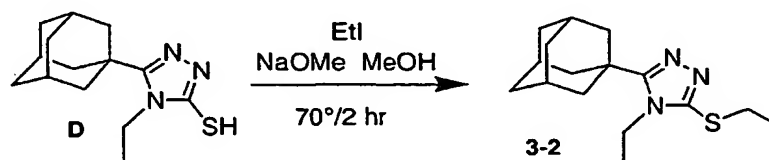
<u>Ex.</u>	<u>Structure</u>	<u>Name</u>	<u>Reten- tion Time (min)</u>	<u>MS ESI (m/z)</u>
<u>2-1</u>		3-[(3,5,7-trimethyl-1-adamantyl)methyl]-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyridine trifluoroacetate salt	1.982	313.89
<u>2-2</u>		3-(1-adamantyl)-5,6,7,8,9,10-hexahydro[1,2,4]triazolo[4,3-a]azocine trifluoroacetate salt	1.590	285.7
<u>2-3</u>		3-(1-adamantyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole trifluoroacetate salt	1.254	243.7
<u>2-4</u>		3-(3,5-dimethyl-1-adamantyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole trifluoroacetate salt	1.577	271.92

		azolo[4,3- <i>a</i>]azocine trifluoroacetate salt		
<u>2-11</u>		3-[(3,5,7-trimethyl-1-adamantyl)methyl]-5,6,7,8,9,10-hexahydro[1,2,4]triazolo[4,3- <i>a</i>]azocine trifluoroacetate salt	2.126	341.0
<u>2-12</u>		3-(3,5-dimethyl-1-adamantyl)-5,6,7,8,9,10-hexahydro[1,2,4]triazolo[4,3- <i>a</i>]azocine trifluoroacetate salt	1.874	313.9
<u>2-13</u>		3-(1-adamantyl)-6,7,8,9,10,11-hexahydro-5H-[1,2,4]triazolo[4,3- <i>a</i>]azonine trifluoroacetate salt	1.709	299.9
<u>2-14</u>		3-(1-adamantylmethyl)-6,7,8,9,10,11-hexahydro-5H-[1,2,4]triazolo[4,3- <i>a</i>]azonine trifluoroacetate salt	1.850	313.8
<u>2-15</u>		3-[(3,5,7-trimethyl-1-adamantyl)methyl]-6,7,8,9,10,11-hexahydro-5H-[1,2,4]triazolo[4,3- <i>a</i>]azonine trifluoroacetate salt	2.220	355.9

A mixture of 1-(1-adamantylcarbonyl)-4-phenylthiosemicarbazide (C) (1.48 g) and 2 N NaOH (45 mL) was heated for 1 h under reflux in a N₂ atmosphere and filtered. The filtrate was acidified with conc HCl to pH 4. The precipitated solid was filtered, washed with water and dried to give 5-(1-adamantyl)-4-phenyl-4H-1,2,4-triazole-3-thiol (11). MS: 312 (M+1).

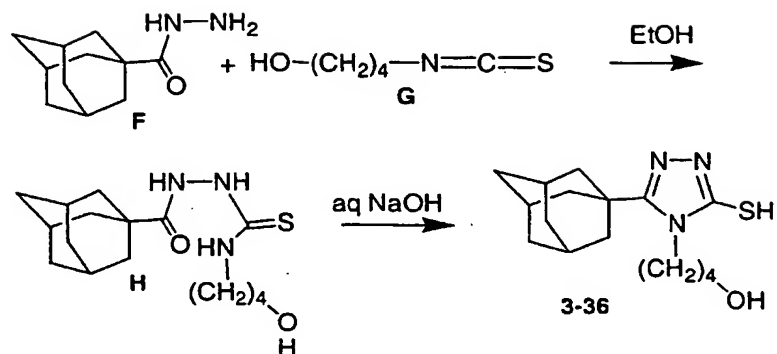
Compounds 3-10, 3-21, 3-22, 3-25, and 3-30 were prepared by essentially the same procedure from 1-adamantylcarbonyl chloride and the appropriate 4-substituted-3-thiosemicarbazide.

10

Procedure 3BPreparation of 3-(1-adamantyl)-4-ethyl-5-(ethylthio)-4H-1,2,4-triazole (3-2)

5-(1-Adamantyl)-4-ethyl-4H-1,2,4-triazole-3-thiol (D, *Arzneim.-Forsch.* 1991, 41, 1260-1264) (40 mg, 0.15 mmol) and 0.5 M methanolic NaOMe (0.3 mL, 0.15 mmol) in methanol (1 mL) was heated under reflux for 10 min. Ethyl iodide (12 μ L, 0.15 mmol) was added, and the mixture was heated under reflux for 2 h. The methanol was removed *in vacuo*, and the residue was partitioned between CH₂Cl₂ and water. The organic layer was dried (MgSO₄) and evaporated *in vacuo*. The residue was purified by chromatography on silica gel with 10% MeOH in CH₂Cl₂ to give 3-(1-adamantyl)-4-ethyl-5-(ethylthio)-4H-1,2,4-triazole (2), MS: 278 (M+1).

Compounds 3-1 through 3-9, 3-12, 3-13, 3-14, 3-23, 3-24, 3-26 through 3-29, 3-31 through 3-35, 3-40, 3-41; 3-48, 3-49 and 3-50 were prepared by essentially the same procedure from the appropriate 4-substituted 5-(1-adamantyl)-4H-1,2,4-triazole-3-thiol and a bromide or iodide.

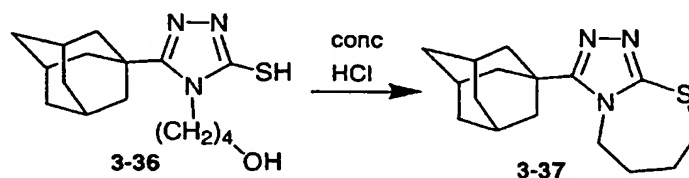
Procedure 3DPreparation of 4-[3-(1-adamantyl)-5-mercapto-4H-1,2,4-triazol-4-yl]butan-1-ol (3-36)

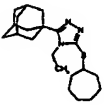
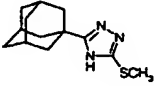
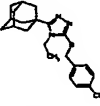
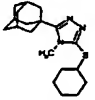
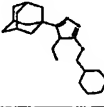
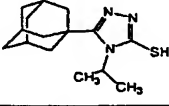
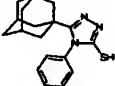
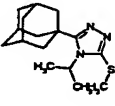
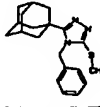
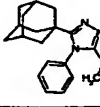
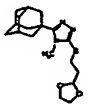
- 5 A mixture of 4-hydroxybutyl isothiocyanate (G, *Synlett*, 1997, 773-774) (300 mg, 2.3 mmol), 1-adamantanecarbonyl hydrazide (388 mg, 2 mmol) in ethanol (6 mL) was heated under reflux for 1.5 h. After standing overnight at room temperature, the solid was filtered, washed with ethanol and dried to give 1-(1-adamantylcarbonyl)-4-(4-hydroxybutyl) thiosemicarbazide (H). MS: 326 (M+1).
- 10 A mixture of 1-(1-adamantylcarbonyl)-4-(4-hydroxybutyl) thiosemicarbazide (H) (471 mg, 1.45 mmol) and 2 N NaOH (12 mL) was heated under reflux in a N₂ atmosphere for 1.5 h. The cooled reaction was acidified with conc. HCl to pH 4. The precipitated solid was filtered, washed with water and dried to give 4-[3-(1-adamantyl)-5-mercapto-4H-1,2,4-triazol-4-yl] butan-1-ol (3-36).
- 15 MS: 308 (M+1).

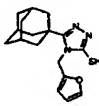
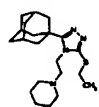
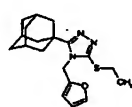
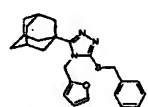
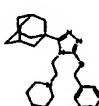
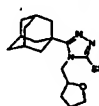
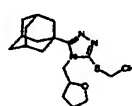
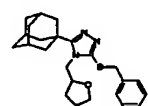
Compound 3-42 was prepared by essentially the same procedure from 1-adamantylcarbonyl hydrazide and 5-hydroxypentyl isothiocyanate.

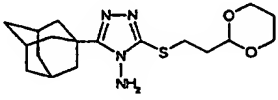
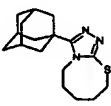
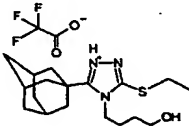
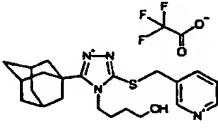
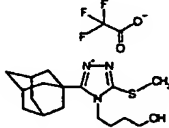
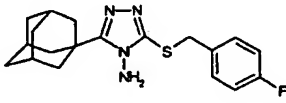
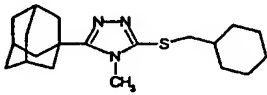
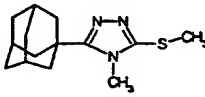
Procedure 3E

20



<u>3-5</u>		3-(1-adamantyl)-5-(cycloheptylthio)-4-ethyl-4H-1,2,4-triazole	3B	360
<u>3-6</u>		3-(1-adamantyl)-5-(methylthio)-4H-1,2,4-triazole	3B	250
<u>3-7</u>		3-(1-adamantyl)-5-[(4-chlorobenzyl)thio]-4-ethyl-4H-1,2,4-triazole	3B	388
<u>3-8</u>		3-(1-adamantyl)-5-(cyclohexylthio)-4-methyl-4H-1,2,4-triazole	3B	332
<u>3-9</u>		3-(1-adamantyl)-5-[(cyclohexylmethyl)thio]-4-ethyl-4H-1,2,4-triazole	3B	360
<u>3-10</u>		5-(1-adamantyl)-4-isopropyl-4H-1,2,4-triazole-3-thiol	3A	278
<u>3-11</u>		5-(1-adamantyl)-4-phenyl-4H-1,2,4-triazole-3-thiol	3A	312
<u>3-12</u>		3-(1-adamantyl)-4-isopropyl-5-(methylthio)-4H-1,2,4-triazole	3B	292
<u>3-13</u>		3-(1-adamantyl)-4-benzyl-5-(methylthio)-4H-1,2,4-triazole	3B	340
<u>3-14</u>		3-(1-adamantyl)-4-phenyl-5-(methylthio)-4H-1,2,4-triazole	3B	326
<u>3-15</u>		3-(1-adamantyl)-5-[(2-(1,3-dioxolan-2-yl)ethyl)thio]-4-methyl-4H-1,2,4-triazole	3C	350

		triazole		
<u>3-25</u>		5-(1-adamantyl)-4-(2-furylmethyl)-4H-1,2,4-triazole-3-thiol	3A	316
<u>3-26</u>		1-{2-[3-(1-adamantyl)-5-(ethylthio)-4H-1,2,4-triazol-4-yl]ethyl}piperidine	3B	375
<u>3-27</u>		3-(1-adamantyl)-5-(ethylthio)-4-(2-furylmethyl)-4H-1,2,4-triazole	3B	344
<u>3-28</u>		3-(1-adamantyl)-5-(benzylthio)-4-(2-furylmethyl)-4H-1,2,4-triazole	3B	406
<u>3-29</u>		1-{2-[3-(1-adamantyl)-5-(benzylthio)-4H-1,2,4-triazol-4-yl]ethyl}piperidine	3B	437
<u>3-30</u>		5-(1-adamantyl)-4-(tetrahydrofuran-2-ylmethyl)-4H-1,2,4-triazole-3-thiol	3A	332
<u>3-31</u>		3-(1-adamantyl)-5-(ethylthio)-4-(tetrahydrofuran-2-ylmethyl)-4H-1,2,4-triazole	3B	348
<u>3-32</u>		3-(1-adamantyl)-5-(benzylthio)-4-(tetrahydrofuran-2-ylmethyl)-4H-1,2,4-triazole	3B	410

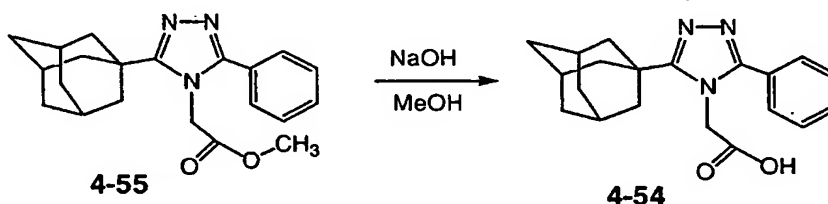
<u>3-43</u>		3-(1-adamantyl)-5-([2-(1,3-dioxan-2-yl)ethyl]thio)-4H-1,2,4-triazol-4-amine	3C	365
<u>3-44</u>		3-(1-adamantyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[3,4-b][1,3]thiazocine	3E	304
<u>3-45</u>		4-[3-(1-adamantyl)-5-(ethylthio)-4H-1,2,4-triazol-4-yl]butan-1-ol trifluoroacetate salt	3C	336*
<u>3-46</u>		4-[3-(1-adamantyl)-5-[(pyridin-3-ylmethyl)thio]-4H-1,2,4-triazol-4-yl]butan-1-ol trifluoroacetate salt	3C	399*
<u>3-47</u>		4-[3-(1-adamantyl)-5-(methylthio)-4H-1,2,4-triazol-4-yl]butan-1-ol trifluoroacetate salt	3C	322*
<u>3-48</u>		3-(1-adamantyl)-5-[(4-fluorobenzyl)thio]-4H-1,2,4-triazol-4-amine	3B	358
<u>3-49</u>		3-(1-adamantyl)-5-[(cyclohexylmethyl)-thio]-4-methyl-4H-1,2,4-triazole	3B	345
<u>3-50</u>		3-(1-adamantyl)-4-methyl-5-(methylthio)-4H-1,2,4-triazole	3B	264
				*free base

Besides the flash chromatography on silica gel and recrystallization described above, the crude reaction mixtures could be purified by preparative TLC on silica gel or by reverse phase HPLC on a C-18 silica gel column using an acetonitrile-0.1% trifluoroacetic acid gradient or by combinations of these procedures.

5 The amide starting materials that were not available commercially were prepared by EDC/DMAP mediated reaction between the appropriate carboxylic acid and amine in methylene chloride. For N-methyl amides, the appropriate methyl ester or the acid chloride was reacted at room temperature with 40% aqueous methylamine.

10

Procedure 4B

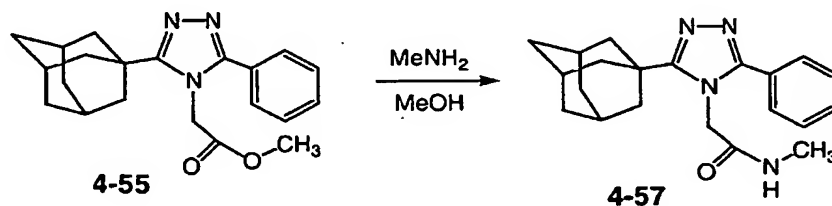


15 Preparation of [3-(1-adamantyl)-5-phenyl-4H-1,2,4-triazol-4-yl]acetic acid (4-54)

Methyl [3-(1-adamantyl)-5-phenyl-4H-1,2,4-triazol-4-yl]acetate (4-55) (15 mg), 0.5 N NaOH (1 mL) and methanol (0.5 mL) were reacted at room temperature for 17 h. The methanol was evaporated *in vacuo*. The aqueous residue was acidified with acetic acid and extracted ten times with chloroform. The extracts were dried (MgSO₄) and evaporated *in vacuo* to give [3-(1-adamantyl)-5-phenyl-4H-1,2,4-triazol-4-yl]acetic acid (4-54). MS: 338 (M+1).

20

Procedure 4C



25

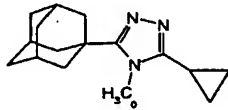
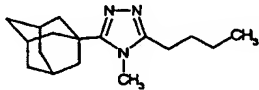
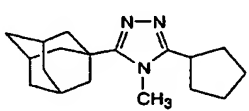
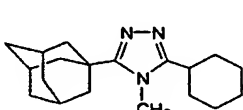
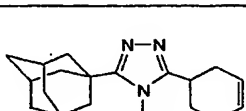
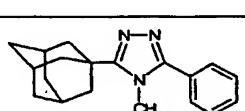
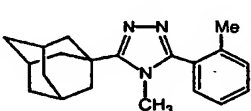
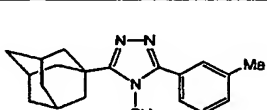
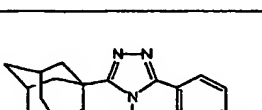
methylene chloride (3x) and the combined extracts washed with water, dried (MgSO₄) and concentrated *in vacuo* to give *N*'-pentanoyladamantane-1-carbohydrazide (G). ¹H NMR (CDCl₃): δ 0.94 (t, 3H); 1.38 (m, 2H); 1.75 (m, 8H); 1.93 (d, 6H); 2.08 (s, 3H); 2.29 (t, 2H); 8.47 (d, 1H); 8.7 (d, 1H).

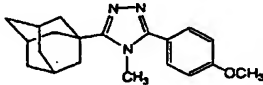
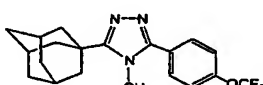
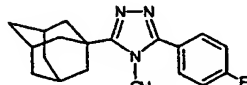
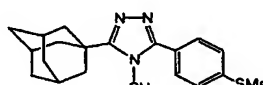
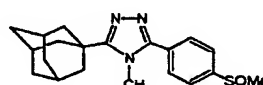
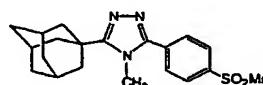
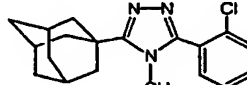
- 5 Thionyl chloride (0.71 mL, 9.6 mmol) was added dropwise to a mixture of *N*'-pentanoyladamantane-1-carbohydrazide (G) (2.06 g, 7.4 mmol) and pyridine (1.55 mL, 9.2 mmol) at 0°C. After stirring at 0°C for 2.5 h, the mixture was filtered and concentrated *in vacuo*. Toluene (40 mL) was added and the solution refluxed for 3.5 h. The mixture was concentrated *in vacuo* and the residue purified by
10 flash chromatography on silica gel with hexane-ethyl acetate (4:1) to give 2-(1-adamantyl)-5-butyl-1,3,4-oxadiazole (H). MS: 261 (M+1).

- The oxadiazoles used for the preparation of compounds 4-2, 4-3, 4-4, 4-48, 4-50, 4-58, 4-61, 4-62, 4-63, 4-65, 4-70, 4-71, 4-75, 4-78, 4-88, 4-90, 4-91, 4-98, 4-100, and 4-109 are prepared essentially by the same procedure from
15 adamantane-1-carbohydrazide and the appropriate acid chloride.

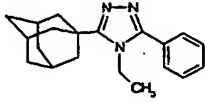
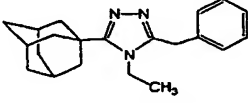
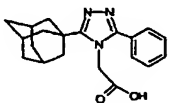
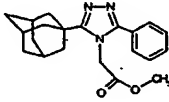
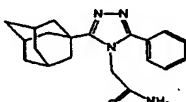
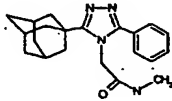
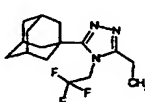
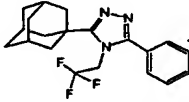
- 2-(1-Adamantyl)-5-propyl-1,3,4-oxadiazole (I) (49 mg, 0.2 mmol) and methylammonium trifluoroacetate (290 mg, 2 mmol, prepared by combining equimolar amounts of methylamine and trifluoroacetic acid in ether followed by concentration *in vacuo*) were stirred together in a sealed vial at 150° for 18 h. The
20 residue was partitioned with methylene chloride and water, the organic layer washed with 10% K₂CO₃ and brine. The aqueous phase was extracted with methylene chloride (6x), the combined extracts dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by reverse phase HPLC on a C-18 silica gel column using an acetonitrile-0.1% trifluoroacetic acid gradient to afford 3-(1-adamantyl)-4-methyl-5-propyl-4H-1,2,4-triazole (4-3). MS: 260 (M+1).
25

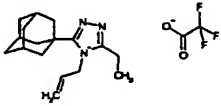
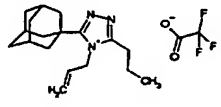
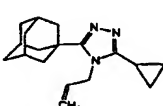
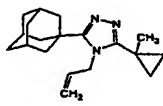
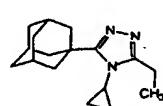
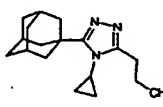
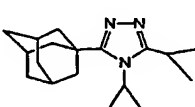
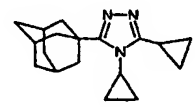
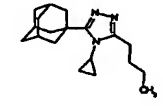
Compounds 4-2, 4-3, 4-4, 4-48, 4-50, 4-58, 4-61, 4-62, 4-63, 4-65, 4-70, 4-71, 4-75, 4-78, 4-88, 4-90, 4-91, 4-98, 4-100, and 4-109 are prepared essentially by the same procedure from an 1,3,4-oxadiazole and the appropriate amine trifluoroacetate salt.

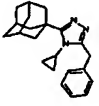
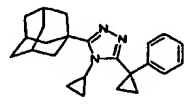
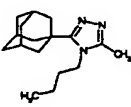
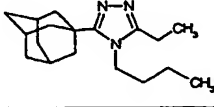
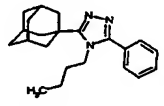
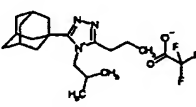
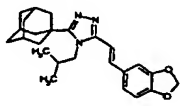
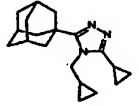
<u>4-5</u>		3-(1-adamantyl)-4-methyl-5-cyclopropyl-4H-1,2,4-triazole	4A	258
<u>4-6</u>		3-(1-adamantyl)-5-butyl-4-methyl-4H-1,2,4-triazole	4A	274
<u>4-7</u>		3-(1-adamantyl)-5-cyclopentyl-4-methyl-4H-1,2,4-triazole	4A	286
<u>4-8</u>		3-(1-adamantyl)-5-cyclohexyl-4-methyl-4H-1,2,4-triazole	4A	300
<u>4-9</u>		3-(1-adamantyl)-5-cyclohex-3-en-1-yl-4-methyl-4H-1,2,4-triazole	4A	298
<u>4-10</u>		3-(1-adamantyl)-5-phenyl-4-methyl-4H-1,2,4-triazole	4A	294
<u>4-11</u>		3-(1-adamantyl)-4-methyl-5-(2-methylphenyl)-4H-1,2,4-triazole	4A	308
<u>4-12</u>		3-(1-adamantyl)-4-methyl-5-(3-methylphenyl)-4H-1,2,4-triazole	4A	308
<u>4-13</u>		3-(1-adamantyl)-4-methyl-5-(4-methylphenyl)-4H-1,2,4-triazole	4A	308

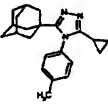
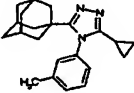
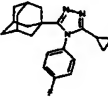
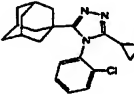
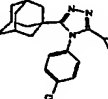

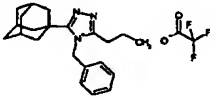

<u>4-20</u>		3-(1-adamantyl)-5-(4-methoxyphenyl)-4-methyl-4H-1,2,4-triazole	4A	324
<u>4-21</u>		3-(1-adamantyl)-4-methyl-5-[4-(trifluoromethoxy)phenyl]-4H-1,2,4-triazole	4A	378
<u>4-22</u>		3-(1-adamantyl)-4-methyl-5-(4-fluorophenyl)-4H-1,2,4-triazole	4A	312
<u>4-23</u>		3-(1-adamantyl)-4-methyl-5-[4-(methylthio)phenyl]-4H-1,2,4-triazole	4A	312
<u>4-24</u>		3-(1-adamantyl)-4-methyl-5-[4-(methylsulfinyl)phenyl]-4H-1,2,4-triazole	4F	356
<u>4-25</u>		3-(1-adamantyl)-4-methyl-5-[4-(methylsulfonyl)phenyl]-4H-1,2,4-triazole	4A	372
<u>4-26</u>		3-(1-adamantyl)-4-methyl-5-(2-chlorophenyl)-4H-1,2,4-triazole	4A	328

<u>4-35</u>		3-(1-adamantyl)-4-methyl-5-tetrahydro-2H-pyran-4-yl-4H-1,2,4-triazole	4A	302
<u>4-36</u>		3-(1-adamantyl)-5-(2-thienyl)-4-methyl-4H-1,2,4-triazole	4A	300
<u>4-37</u>		3-(1-adamantyl)-5-(5-chlorothiophen-2-yl)-4-methyl-4H-1,2,4-triazole	4A	334
<u>4-38</u>		3-(1-adamantyl)-5-(3-chlorothiophen-2-yl)-4-methyl-4H-1,2,4-triazole	4A	334
<u>4-39</u>		3-(1-adamantyl)-5-(3-thienyl)-4-methyl-4H-1,2,4-triazole	4A	300
<u>4-40</u>		3-(1-adamantyl)-5-(2,3-dihydro-1-benzofuran-5-yl)-4-methyl-4H-1,2,4-triazole	4A	336
<u>4-41</u>		3-(1-adamantyl)-5-benzyl-4-methyl-4H-1,2,4-triazole	4A	308
<u>4-42</u>		3-(1-adamantyl)-5-(3-fluorobenzyl)-4-methyl-4H-1,2,4-triazole	4A	326

<u>4-52</u>		3-(1-adamantyl)-5-phenyl-4-ethyl-4H-1,2,4-triazole	4A	308
<u>4-53</u>		3-(1-adamantyl)-5-benzyl-4-ethyl-4H-1,2,4-triazole	4A	322
<u>4-54</u>		[3-(1-adamantyl)-5-phenyl-4H-1,2,4-triazol-4-yl]acetic acid	4B	338
<u>4-55</u>		methyl [3-(1-adamantyl)-5-phenyl-4H-1,2,4-triazol-4-yl]acetate	4A	352
<u>4-56</u>		2-[3-(1-adamantyl)-5-phenyl-4H-1,2,4-triazol-4-yl]acetamide	4C	337
<u>4-57</u>		2-[3-(1-adamantyl)-5-phenyl-4H-1,2,4-triazol-4-yl]-N-methylacetamide	4C	351
<u>4-58</u>		3-(1-adamantyl)-5-ethyl-4-(2,2,2-trifluoroethyl)-4H-1,2,4-triazole	4A	314
<u>4-59</u>		3-(1-adamantyl)-5-phenyl-4-(2,2,2-trifluoroethyl)-4H-1,2,4-triazole	4A	362

<u>4-70</u>		3-(1-adamantyl)-4-allyl-5-ethyl-4H-1,2,4-triazole	4D	272 (free base)
<u>4-71</u>		3-(1-adamantyl)-4-allyl-5-propyl-4H-1,2,4-triazole	4D	286 (free base)
<u>4-72</u>		3-(1-adamantyl)-4-allyl-5-cyclopropyl-4H-1,2,4-triazole	4A	284
<u>4-73</u>		3-(1-adamantyl)-4-allyl-5-(1-methylcyclopropyl)-4H-1,2,4-triazole	4A	298
<u>4-74</u>		3-(1-adamantyl)-4-cyclopropyl-5-ethyl-4H-1,2,4-triazole	4A	272
<u>4-75</u>		3-(1-adamantyl)-4-cyclopropyl-5-propyl-4H-1,2,4-triazole	4D	286
<u>4-76</u>		3-(1-adamantyl)-4-cyclopropyl-5-isopropyl-4H-1,2,4-triazole	4A	362
<u>4-77</u>		3-(1-adamantyl)-4,5-dicyclopropyl-4H-1,2,4-triazole	4A	284
<u>4-78</u>		3-(1-adamantyl)-4-cyclopropyl-5-butyl-4H-1,2,4-triazole	4A	300

<u>4-86</u>		3-(1-adamantyl)-4-cyclopropyl-5-benzyl-1,2,4-triazole	4A	334
<u>4-87</u>		3-(1-adamantyl)-4-cyclopropyl-5-(1-phenylcyclopropyl)-1,2,4-triazole	4A	360
<u>4-88</u>		3-(1-adamantyl)-5-methyl-4-butyl-1,2,4-triazole	4D	274
<u>4-89</u>		3-(1-adamantyl)-5-ethyl-4-butyl-1,2,4-triazole	4A	288
<u>4-90</u>		3-(1-adamantyl)-5-phenyl-4-butyl-1,2,4-triazole	4D	336
<u>4-91</u>		3-(1-adamantyl)-4-isobutyl-5-propyl-1,2,4-triazole	4D	302 (free base)
<u>4-92</u>		3-(1-adamantyl)-5-[(E)-2-(1,3-benzodioxol-5-yl)ethenyl]-4-isobutyl-1,2,4-triazole	4A	406
<u>4-93</u>		3-(1-adamantyl)-5-cyclopropyl-4-(cyclopropylmethyl)-1,2,4-triazole	4A	298

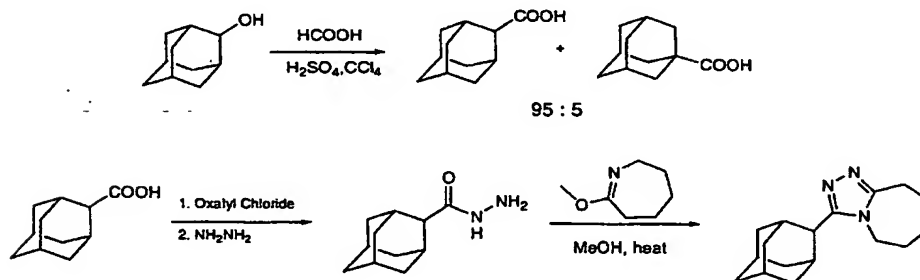
<u>4-103</u>		3-(1-adamantyl)-5-cyclopropyl-4-(4-methylphenyl)-4H-1,2,4-triazole	4A	334
<u>4-104</u>		3-(1-adamantyl)-5-cyclopropyl-4-(3-methylphenyl)-4H-1,2,4-triazole	4A	334
<u>4-105</u>		3-(1-adamantyl)-5-cyclopropyl-4-(4-fluorophenyl)-4H-1,2,4-triazole	4A	338
<u>4-106</u>		3-(1-adamantyl)-5-cyclopropyl-4-(2-chlorophenyl)-4H-1,2,4-triazole	4A	354
<u>4-107</u>		3-(1-adamantyl)-5-cyclopropyl-4-(4-chlorophenyl)-4H-1,2,4-triazole	4A	354
<u>4-108</u>		3-(1-adamantyl)-5-cyclopropyl-4-(2,4-dimethylphenyl)-4H-1,2,4-triazole	4A	348
<u>4-109</u>		3-(1-adamantyl)-4-benzyl-5-propyl-4H-1,2,4-triazole	4D	336 (free base)
<u>4-110</u>		3-(1-adamantyl)-4-benzyl-5-cyclopropyl-4H-1,2,4-triazole	4A	334

magnesium sulfate, filtered and evaporated to dryness to give crude 3,5-dimethyladamantaneacetic acid (6.23 g).

3,5-Dimethyladamantaneacetic acid (1.515 g) was dissolved in methylene chloride (50 mL) and stirred at room temperature under nitrogen. Oxalyl chloride (2.38 mL) was added and the reaction was stirred for 2 h whereupon all of the volatiles were removed. The crude acid chloride was dissolved in THF (30 mL) and added to a stirring solution of hydrazine (5 mL), methanol (5 mL), and THF (5 mL). The methanol and THF were removed by evaporation and the remaining liquid was added to aqueous NaOH (1N) and extracted with ethyl acetate (4X). The organic layers were combined, dried over magnesium sulfate, filtered and evaporated to give 2-(3,5-dimethyl-1-adamantyl)acetohydrazide as a clear thick oil (1.60 g).

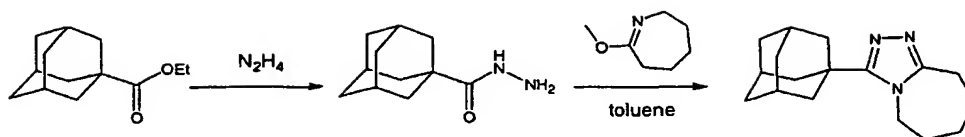
The acyl hydrazide (0.85 g), 1-aza-2-methoxy-1-cycloheptene (559 mg) and anhydrous methanol (10 mL) were added to a flask, warmed to 40 °C and stirred for 1 h. The solution was warmed to 50 °C for 1 h then refluxed overnight. After cooling, the methanol was evaporated and the crude product was purified by column chromatography (silica gel, 100% Ethyl acetate → 10% methanol/ ethyl acetate → 10% methanol/CH₂Cl₂).

EXAMPLE 5-2



Preparation of 3-adamantan-2-yl-4H,5H,6H,7H,8H-1,2,4-triazolo[4,3-a]perhydroazepine (5-2)

Concentrated sulfuric acid (50 mL) and carbon tetrachloride (100 mL) were combined, cooled to 0 °C and vigorously stirred. Adamantan-2-ol (451 mg) was dissolved in 96% formic acid (6 mL) and the solution was added to the sulfuric acid over 1 hour. The reaction continued to stir at 0 °C for 90 min after which it was

EXAMPLE 5-45 Preparation of 3-adamantanyl-1H,4H,5H,6H,7H,8H-1,2,4-triazolo[4,5-f]azepine (5-4)

A mixture of ethyl 1-adamantanecarboxylate (236.6 g, 1.14 mol), hydrazine hydrate (500 g, about 8.5 mol) and diethylene glycol (2 kg) was refluxed for about 65 h. The solution was allowed to cool to room temperature and aged for 10 days. The resulting suspension was poured into water (6 L) with stirring. The resulting slurry was filtered, and the cake washed with water (900 mL). The cake was re-slurried with water (1 L), filtered and the cake washed with water (1 L) and hexanes (2 L). The solid was air-dried affording 191.7 g of off-white crystalline material.

The hydrazide from above, (90 g, 0.46 mole), 1-aza-2-methoxy-1-cycloheptene (75 mL, 66.5 g, 0.52 mol), acetic acid (1 mL) and toluene (1.35 L) were combined under nitrogen and stirred mechanically. The reaction gradually thickened as a white solid formed. After 20 min, additional toluene (200 mL) was added. The reaction continued to thicken and after another 5 min, additional toluene (300 mL) was added. The reaction thickened and was aged an additional 15 min without agitation. The reaction was diluted with toluene (500 mL) and hexanes (2.5 L), stirred for 5 min then filtered. The cake was washed with 1:1 toluene/hexanes (2 X 350 mL), followed by hexanes (1 L). While the cake was still damp, it was transferred to a flask fitted with a simple distillation head. Toluene (2 L) and acetic acid (1 mL) were added and the mixture heated. Slow distillation of the mixture afforded 500 mL of distillate collected over 1 h, with a distillate temperature of 104°C attained. The solution was cooled and concentrated on a rotary evaporator to a thick slurry (about 200 mL). This was diluted with ether (about 300 mL) and filtered. The cake was washed with 3:1 ether/toluene, ether and dried affording 106.7 g of semi-pure material.

A 24 g sample of comparable semi-pure material obtained from a smaller run was combined with the two crops above and chromatographed (silica 85:15:1 ether/methanol/NH₄OH). The product cuts were concentrated, and the

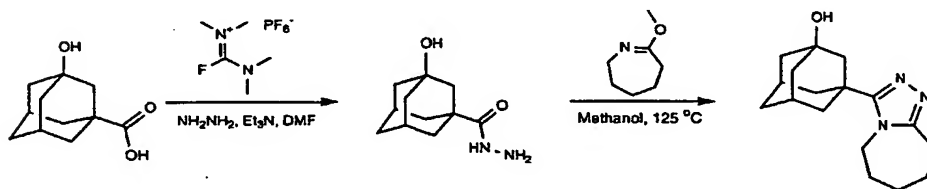
Preparation of 3-(3,5,8-trimethyladamantanyl)-4H,5H,6H,7H,8H-1,2,4-triazolo[4,3-a]perhydroazepine (5-6)

3,5,7-Trimethyladamantane-1-carboxylic acid was dissolved in DMF (2 mL) and stirred at room temperature under nitrogen. Triethylamine (0.093 mL),
 5 and fluoro-N,N,N',N'-tetramethylformamidium hexafluorophosphate (88 mg) were added. After 10 min, hydrazine hydrate (0.033 mL) was added and, after stirring for 15 min, water (2 mL) was added. The crude acyl hydrazide was collected by filtration.

3,5,7-Trimethyladamantane-1-carbohydrazide (26.2 mg), 1-aza-2-methoxy-1-cycloheptene (16 μ L) and anhydrous toluene (1 mL) were added to a small
 10 vial and heated to 50 °C for 3 h. The solution was then heated to 120 °C for 4 h. After cooling, the toluene was evaporated and the product was purified by column chromatography (silica gel, 100% Ethyl acetate \rightarrow 10% methanol/ethyl acetate \rightarrow 10% methanol/CH₂Cl₂).

15

EXAMPLE 5-7



20 Preparation of 3-(4H,5H,6H,7H,8H-1,2,4-triazolo[4,5-a]perhydroazepin-3-yl)adamantan-1-ol (5-7)

3-Hydroxyadamantan-1-carboxylic acid was dissolved in DMF (3 mL) and stirred at room temperature under nitrogen. Triethylamine (0.33 mL), and
 25 fluoro-N,N,N',N'-tetramethylformamidium hexafluorophosphate (296 mg) were added. After 10 min, hydrazine hydrate (0.114 mL) was added and after stirring for 15 min the reaction was evaporated to dryness. The crude 3-hydroxyadamantan-1-carbohydrazide, 1-aza-2-methoxy-1-cycloheptene (0.2 mL) and anhydrous methanol (6 mL) were added to a small flask and heated to 50 °C for 3 h. The solution was then heated to 70 °C for 24 h. After cooling, the methanol was evaporated and the product
 30 was purified by column chromatography (silica gel, 100% Ethyl acetate \rightarrow 10% methanol/ethyl acetate \rightarrow 10% methanol/CH₂Cl₂).

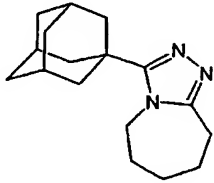
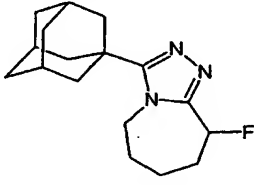
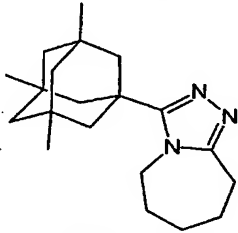
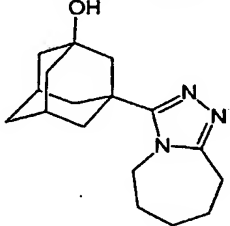
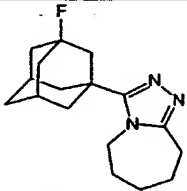
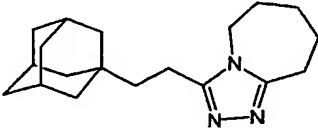
was added and the reaction was stirred 36 h. The solution was washed with saturated aqueous sodium bicarbonate and extracted with ether (2X). The ether layers were combined, dried with magnesium sulfate and the solvent removed. The product was purified by silica gel chromatography (10% ethyl acetate/Hexane to 20% ethyl acetate/Hexane) to give 72.3 mg of the desired diazoketone.

The diazoketone was dissolved in THF (3 mL) and water (6 mL) and stirred at room temperature. Silver nitrate (67 mg) was added and the reaction was stirred in the dark for 15 h. The solution was added to additional water (10 mL) and extracted with ethyl acetate (2X). The organic layers were combined, dried (magnesium sulfate), filtered and the solvent evaporated. The product was purified by silica gel chromatography (20:79:1 ethyl acetate:hexanes:acetic acid → 30:69:1 ethyl acetate:hexanes:acetic acid → 50:49:1 ethyl acetate:hexanes:acetic acid) and provided 45 mg of the desired carboxylic acid.

The carboxylic acid (45 mg) was dissolved in dry methylene chloride and under nitrogen stirred at room temperature. Oxalyl chloride (0.100 mL) was added and the solution was stirred for 2 h whereupon the product was dried *in vacuo*. The acid chloride was dissolved in tetrahydrofuran (2 mL) and rapidly added to a solution of hydrazine (1 mL), THF (1 mL) and methanol (1 mL) which was stirred under nitrogen and cooled to 0 °C. After slowly warming to room temperature the reaction was dried *in vacuo*. The crude product was added to ethyl acetate and extracted with saturated sodium chloride solution containing about 2% sodium hydroxide. After extraction (2X), the organic layers were combined, dried (magnesium sulfate), filtered and the solvent evaporated. After thorough drying, the crude acyl hydrazide was dissolved in dry methanol (5 mL). 1-Aza-2-methoxy-1-cycloheptene (48 µL) was added and the solution was stirred at 50 °C overnight and 70 °C for 48 h. The solution was evaporated to dryness and purified by preparative HPLC. The resulting trifluoroacetate salt was neutralized by adding to a saturated sodium bicarbonate solution and extracting with ethyl acetate. The purified product was dried over magnesium sulfate, filtered and evaporated to dryness.

Preparative LC Method:

Column:	YMC – PACK ODS, 100 mm X 20 mm, 5.0 µm
Eluent A:	0.05% TFA in Water
35 Eluent B:	0.05% TFA in Acetonitrile

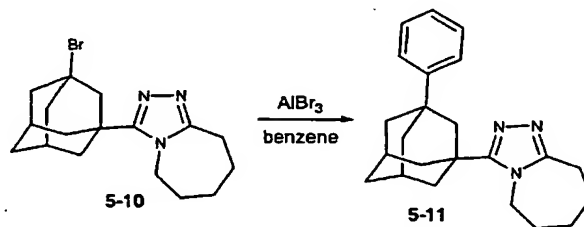
<u>5-4</u>		3-(1-adamantyl)- 6,7,8,9-tetrahydro- 5H- [1,2,4]triazolo[4,3- a]azepine	2.05	272.2
<u>5-5</u>		3-(1-adamantyl)-9- fluoro-6,7,8,9- tetrahydro-5H- [1,2,4]triazolo[4,3- a]azepine	2.23	290.2
<u>5-6</u>		3-(3,5,7-trimethyl- 1-adamantyl)- 6,7,8,9-tetrahydro- 5H- [1,2,4]triazolo[4,3- a]azepine	2.82	314.3
<u>5-7</u>		3-(6,7,8,9- tetrahydro-5H- [1,2,4]triazolo[4,3- a]azepin-3- yl)adamantan-1-ol	1.22	288.2
<u>5-8</u>		3-(3-fluoro-1- adamantyl)-6,7,8,9- tetrahydro-5H- [1,2,4]triazolo[4,3- a]azepine	1.84	290.2
<u>5-9</u>		3-[2-(1- adamantyl)ethyl]- 6,7,8,9-tetrahydro- 5H- [1,2,4]triazolo[4,3- a]azepine	2.66	300.3

added and the solution was stirred at room temperature for 1 h whereupon the solution was evaporated to dryness. The crude acid chloride was dissolved in 10 mL DMF and added dropwise to a stirring solution of DMF (10 mL) and hydrazine (1.04 mL) at room temperature. Water was added and the solution was filtered. The filtrate was extracted with methylene chloride and the solid product was purified by silica gel chromatography (5% methanol in methylene chloride) to give 489 mg of the desired 3-bromoadamantanecarbohydrazide.

To a dry flask was added 480 mg 3-bromoadamantanecarbohydrazide and 12 mL anhydrous methanol. After 5 min, the imino ether (0.504 mL) was added dropwise. The solution was stirred under nitrogen at room temperature for 40 min, warmed to 41 °C for two h, and refluxed for 24 h. The solution was cooled and evaporated to dryness. Purification with silica gel (50/49.9/0.1, ethyl acetate/methylene chloride/ acetic acid) provided 559 mg of the title compound.

15

EXAMPLE 5-11



Preparation of 3-(3-phenyladamantan-1-yl)-4H,5H,6H,7H,8H-1,2,4-triazolo[4,3-a]perhydroazepine (5-11)

65.4 mg of Aluminum tribromide was placed in a dry 10-mL flask. 0.5 mL dry benzene was added and the mixture was cooled in an ice bath. 25 mg of compound 5-10 was rapidly added and the solution was slowly warmed to room temperature and stirred for an additional 18 h. The reaction was quenched with ice and acidified with 2N HCl. The organic layer was separated and washed with water (2X) and brine. The organic solution was dried over magnesium sulfate, filtered and evaporated. The crude product was purified by preparative HPLC to provide 5-11 as its trifluoroacetate salt.

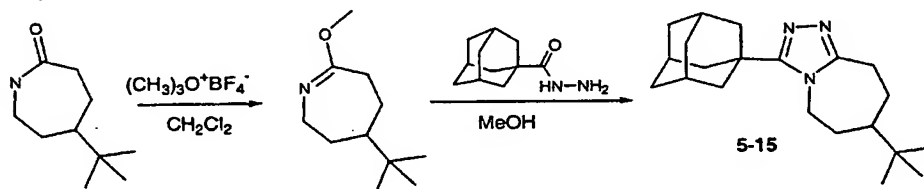
EXAMPLES 5-13 AND 5-14

The reaction sequence was repeated in similar fashion starting with cycloundecanone and cyclononanone to prepare 3-adamantanyl-

- 5 4,5,6,7,8,9,10,11,12,13,3a-undecahydro-1,2,4-triazolo[4,3-a][12]annulene (5-13) and 3-adamantanyl-4H,5H,6H,7H,8H,9H,10H,11H-1,2,4-triazolo[4,3-a]perhydroazepine (5-14), respectively.

EXAMPLE 5-15

10



Preparation of 3-Adamantanyl-6-(tert-butyl)-4H,5H,6H,7H,8H-1,2,4-triazolo[4,3-a]perhydroazepine (5-15)

- 15 5-*tert*-Butylazocan-2-one (30 mg) was dissolved in 2 mL methylene chloride and stirred at room temperature under nitrogen. 31.3 g Trimethyloxonium tetrafluoroborate was added and the reaction stirred overnight. The mixture was added to saturated aqueous sodium bicarbonate and extracted with methylene chloride (2X). The combined organic layers were washed with brine, dried over magnesium sulfate, and the solvent evaporated to provide crude 5-*tert*-butyl-8-methoxy-2,3,4,5,6,7-hexahydroazocine.
- 20

- 25 Adamantanecarbohydrazide (30 mg) was added to a small dry flask and dissolved in 3 mL dry methanol. The crude 5-*tert*-butyl-8-methoxy-2,3,4,5,6,7-hexahydroazocine was added and the mixture was refluxed at 70 °C overnight. The methanol was removed by evaporation and 3 mL toluene added. This mixture was refluxed 24 h at 122 °C. The toluene was evaporated and the resulting solid was purified by preparative HPLC (100% gradient/12min) to provide 5-15 as the trifluoroacetate salt.

- 30 The reaction sequence was carried out in a similar manner to prepare the compounds of Examples 5-16 through 5-20 listed in the table below:

Gradient: 10 % B to 100 % B : between 10 and 20 min, hold at 100 % B for an additional 1.0 min, ramp back from 100% B to 10 % B in 0.5 min

Flow: 20 mL/min

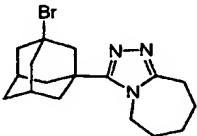
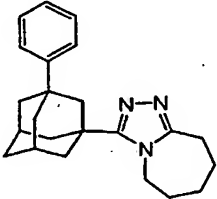
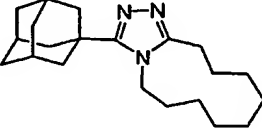
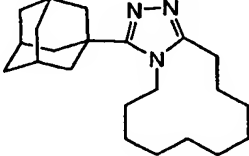
5 Column Temperature: ambient

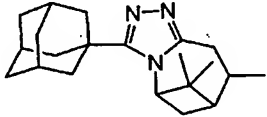
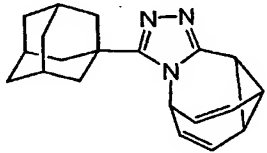
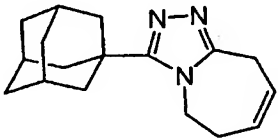
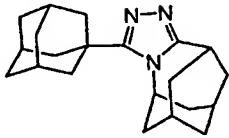
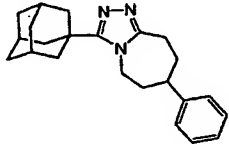
Injection amount: 5.0 mL

Detection: photodiode array

Table

10

<u>Ex.</u>	<u>Structure</u>	<u>Name</u>	<u>Retention Time (min)</u>	<u>MS ESI (m/z)</u>
<u>5-10</u>		3-(3-bromo-1-adamantyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine	2.42	350.3
<u>5-11</u>		3-(3-phenyl-1-adamantyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4,3-a]azepine trifluoroacetate salt	2.96	348.3
<u>5-12</u>		3-(1-adamantyl)-6,7,8,9,10,11,12,13-octahydro-5H-[1,2,4]triazolo[4,3-a]azacycloundecine trifluoroacetate salt	3.09	328.3
<u>5-13</u>		3-(1-adamantyl)-5,6,7,8,9,10,11,12,13,14-decahydro[1,2,4]triazolo[4,3-a]azepine	3.28	342.3

<u>5-19</u>		3-(1-adamantyl)- 6,6,8-trimethyl- 6,7,8,9-tetrahydro- 5H-5,7- methano[1,2,4]triazolo[4,3-a]azepine trifluoroacetate salt	2.69	326.3
<u>5-20</u>		3-(1-adamantyl)- 5,7a,8,8a- tetrahydro-5,8- ethenocyclopropa[c] [1,2,4]triazolo[4,3-a]azepine trifluoroacetate salt	2.48	306.3
<u>5-21</u>		3-(1-adamantyl)- 6,9-dihydro-5H- [1,2,4]triazolo[4,3-a]azepine trifluoroacetate salt	2.05	270.2
<u>5-22</u>		3-(1-adamantyl)- 6,7,8,9,10,11- hexahydro-5H- 5,9:7,11- dimethano[1,2,4]triazolo[4,3-a]azonine trifluoroacetate salt	2.40	324.3
<u>5-23</u>		3-(1-adamantyl)-7- phenyl-6,7,8,9- tetrahydro-5H- [1,2,4]triazolo[4,3-a]azepine trifluoroacetate salt	2.72	348.2

dimethylaminopropyl)carbodiimide hydrochloride (EDC, 95 mg, 0.49 mmol). The mixture was stirred at room temperature under nitrogen for 2 h, then added to a separatory funnel containing 50 mL of ethyl acetate and aqueous hydrochloric acid (HCl, 1N). The layers were separated and the organic layer was washed sequentially
5 with aqueous N HCl, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over anhydrous sodium sulfate and evaporated *in vacuo* to yield 82 mg of title compound as a white powder which was used without purification.

b) Preparation of methyl 2-[2-(4-chlorophenyl)-2-adamantyl]ethanimidoate (6-1b)

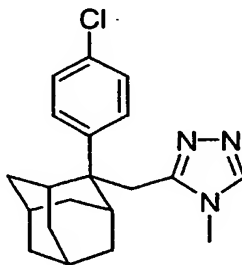
10 A solution of 6-1a (30 mg, 0.1 mmol) in 0.5 mL of anhydrous methylene chloride was treated with trimethyloxonium tetrafluoroborate (30 mg, 0.2 mmol). The mixture was stirred under nitrogen for 18 h, then added to a separatory funnel containing 25 mL of methylene chloride and saturated aqueous sodium bicarbonate solution. The layers were mixed and separated and the organic layer was
15 dried over anhydrous sodium sulfate and evaporated *in vacuo* to yield 32 mg of title compound, which was used without purification.

c) Preparation of 3-([2-(4-chlorophenyl)adamantan-2-yl]methyl)-4H-1,2,4-triazole

20 A solution of 6-1b (32 mg, 0.1 mmol) and formic hydrazide (9 mg, 0.15 mmol) in anhydrous toluene was refluxed under nitrogen for 18 h. The mixture was evaporated to dryness and the residue purified by reverse phase HPLC to give title compound as a white powder.

EXAMPLE 6-2

25



Preparation of 3-([2-(4-chlorophenyl)adamantan-2-yl]methyl)-4-methyl-1,2,4-triazole (6-2)

HPLC Conditions:

Analytical LC Method:

5
Column: MetaChem Polaris C-18A, 30 mm X 4.6 mm, 5.0 μ m
Eluent A: 0.1% TFA in Water
Eluent B: 0.1 % TFA in Acetonitrile
Gradient: 5 % B to 95 % B in 3.3 min, ramp back to 5 % B in 0.3
10 min
Flow: 2.5 mL/min
Column Temperature: 50 $^{\circ}$ C
Injection amount: 5 μ l of undiluted crude reaction mixture.
Detection: DAD: 190-600 nm
15 MS: API-ES ionization mode, mass scan range (100-600)
ELSD: Light Scattering Detector

Preparative LC Method:

20
Column: YMC – PACK ODS, 100 mm X 20 mm, 5.0 μ m
Eluent A: 0.1% TFA in Water
Eluent B: 0.1 % TFA in Acetonitrile
Pre-inject Equilibration: 1.0 min
25 Post-Inject Hold: 1.0 min
Gradient: 10 % B to 100 % B in 7.5 min, hold at 100 % B for an
additional 1.0 min, ramp back from 100% B o 10 % B
in 1.5 min
Flow: 20 mL/min
30 Column Temperature: ambient
Injection amount: 2.0 mL of crude reaction mixture.
Detection: UV at 220 nm.

δ 5.82 (m, 1H), 5.50 (m, 1H), 4.62 (br t, 2H, J = 6.9 Hz), 3.69 (br t, 2H, J = 6.9 Hz), 2.85 (br apparent q, 2H, J = 5.7 Hz, 6.7 Hz), 2.72 (br apparent q, 2H, J = 6.7 Hz, 6.9 Hz), 2.18 (br s, 3H), 2.13 (br s, 6H), 1.82 (AB pattern, 6H, J = 15.8 Hz, J = 12.3 Hz).
Mass spectrum (electrospray): 284 (M + 1).

5

EXAMPLE OF A PHARMACEUTICAL FORMULATION

As a specific embodiment of an oral composition of a compound of the present invention, 50 mg of any of Examples 1 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gelatin capsule.

10

While the invention has been described and illustrated in reference to specific embodiments thereof, those skilled in the art will appreciate that various changes, modifications, and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred doses as set forth hereinabove may be applicable as a consequence of variations in the responsiveness of the human being treated for a particular condition. Likewise, the pharmacologic response observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended therefore that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

15
20

CH₂CONHR^a,
 (CH₂)₀₋₂C₃₋₉ cycloalkyl,
 (CH₂)₀₋₂C₅₋₁₂ bicycloalkyl,
 (CH₂)₀₋₂adamantyl, and
 5 (CH₂)₀₋₂R;

wherein said C₃₋₉ cycloalkyl and C₅₋₁₂ bicycloalkyl optionally have one to two double bonds, and said C₃₋₉ cycloalkyl, C₅₋₁₂ bicycloalkyl, and adamantyl are unsubstituted or substituted with one to six substituents independently selected from (a) zero to five halogens, CH₃, CF₃, OCH₃, and OCF₃, and (b) zero or one phenyl,
 10 said phenyl being unsubstituted or substituted with one to four groups independently selected from halogen, OCH₃, OCF₃, CH₃, and CF₃;

R³ is selected from the group consisting of

hydrogen,
 15 C₁₋₁₀ alkyl, unsubstituted or substituted with one to six substituents independently selected from zero to five halogens and zero or one group selected from hydroxy and C₁₋₃ alkoxy, said alkoxy group being unsubstituted or substituted with one to three halogens,
 C₂₋₁₀ alkenyl, unsubstituted or substituted with one to six substituents
 20 independently selected from zero to five halogens and zero or one group selected from hydroxy and C₁₋₃ alkoxy, said alkoxy group being unsubstituted or substituted with one to three halogens,
 YC₃₋₉ cycloalkyl,
 YC₅₋₁₂ bicycloalkyl,
 25 Yadamantyl, and
 YR;

wherein said C₃₋₉ cycloalkyl and C₅₋₁₂ bicycloalkyl optionally have one to two double bonds, and said C₃₋₉ cycloalkyl, C₅₋₁₂ bicycloalkyl, and adamantyl are unsubstituted or substituted with one to six substituents independently selected from
 30 (a) zero to five halogens, CH₃, CF₃, OCH₃, and OCF₃, and (b) zero or one phenyl, said phenyl being unsubstituted or substituted with one to four groups independently selected from halogen, OCH₃, OCF₃, CH₃, and CF₃;

C₂₋₆ alkenyl, phenyl, biphenyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyloxycarbonyl, an epoxide group bridging 2 adjacent carbons, and 1,3-dioxolanyl geminally disubstituted onto one carbon of R⁴, wherein each C₁₋₆ alkyl and C₂₋₆ alkenyl is unsubstituted or substituted with one to five substituents independently selected from zero to three
5 halogens and zero to two groups selected from phenyl, C₁₋₆ alkyloxycarbonyl, 1,3-dioxolanyl geminally disubstituted onto one carbon, and CN, and wherein each phenyl, biphenyl, and C₃₋₈ cycloalkyl, either as R^c or as a substituent on R^c, is unsubstituted or substituted with one to three groups independently selected from halogen, CH₃, CF₃, OCH₃, and OCF₃;

10 wherein R⁴ optionally has a fused phenyl ring, a benzodioxinyl ring, or a dihydrobenzodioxinyl ring, said phenyl ring, benzodioxinyl ring, and dihydrobenzodioxinyl ring being unsubstituted or substituted with one to three substituents independently selected from halogen, CH₃, CF₃, OCH₃, and OCF₃; and

15 wherein R⁴, including said optional fused phenyl ring, benzodioxinyl ring, or dihydrobenzodioxinyl ring and including all substituents on R⁴ and said fused phenyl ring, benzodioxinyl ring, or dihydrobenzodioxinyl ring, has no more than 20 carbon atoms;

20 with the provisos that

- (a) when X and W represent single bonds, Z is sulfur, R¹ is unsubstituted adamantyl, and R³ is hydrogen, then R² is not hydrogen, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, tert-butyl, phenyl, CH₂phenyl, or cyclohexyl;
- 25 (b) when X and W represent single bonds, Z is sulfur, R¹ is unsubstituted adamantyl, and R³ is ethyl, 3-propenyl, CH₂phenyl, 4-Cl-CH₂phenyl, or 4-NO₂-CH₂phenyl, then R² is not methyl;
- (c) when X and W represent single bonds, Z is sulfur, R¹ is unsubstituted adamantyl, and R³ is CH₂-(CO)-4-F-phenyl, then R² is not phenyl;
- 30 (d) when X and Z represent single bonds and R¹ is unsubstituted adamantyl, then R² and R³ taken together cannot form a C₃₋₅ alkylene R⁴ bridging group; and
- (e) R² and R³ are not both hydrogen.

R^a is selected from the group consisting of hydrogen and C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five fluorines; and

R³ is selected from the group consisting of

- 5 hydrogen,
 C₁₋₆ alkyl, unsubstituted or substituted with one to five halogens,
 C₂₋₆ alkenyl, unsubstituted or substituted with one to five halogens,
 (CH₂)₀₋₁C₃₋₆ cycloalkyl, wherein cycloalkyl has one double bond and is
unsubstituted or substituted with one to five substituents independently selected from
10 the group consisting of (a) zero to five halogens and methyl and (b) zero or 1 phenyl,
 (CH₂)₀₋₁ adamantyl, unsubstituted or substituted with one to four substituents
independently selected from halogen and methyl,
 (CH₂)₀₋₁ phenyl, unsubstituted or substituted with one to three substituents
independently selected from methyl, cyano, hydroxymethyl, CF₃, OCF₃, hydroxy,
15 OCH₃, halogen and S(O)₀₋₂CH₃, and
 YR, wherein Y is selected from the group consisting of CH₂, (-HC=CH-), and
a bond, and R is selected from the group consisting of benzodioxolane, furan,
thiophene, dihydrobenzofuran, tetrahydrofuran, tetrahydropyran, and indane, wherein
R is unsubstituted or substituted with one to three halogens.

20

5. The compound of Claim 2 wherein

R¹ is adamantyl, unsubstituted or substituted with one to five substituents
independently selected from halogen, OCH₃, OCF₃, CH₃, CF₃, and phenyl, wherein
said phenyl is unsubstituted or substituted with one to three halogens;

25

X is a single bond;

Z is S;

WR² is selected from the group consisting of

30

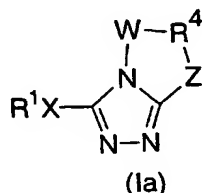
NH₂,

hydrogen,

C₁₋₆ alkyl, unsubstituted or substituted with one to four substituents

independently selected from zero to three halogens and zero or one group selected
from hydroxy and methoxy,

7. The compound of Claim 3 of structural formula Ia



wherein:

5 R^1 is adamantyl, unsubstituted or substituted with one to five substituents independently selected from halogen, OCH_3 , OCF_3 , CH_3 , CF_3 , and phenyl, wherein said phenyl is unsubstituted or substituted with one to three halogens;

X is selected from the group consisting of CH_2 and a single bond;

W and Z are single bonds; and

10

R^4 is

a C₃₋₈ alkylene group, optionally containing one heteroatom selected from O and NR^b between two adjacent carbon atoms of said C₃₋₈ alkylene group, optionally containing one to two carbon-carbon double bonds when R^4 is a C₃₋₈ alkylene group, and optionally also comprising a carbon-carbon single bond connecting two non-adjacent carbon atoms of said C₃₋₈ alkylene group, or

15

a C₄₋₈ cycloalkyl group;

wherein R^b is selected from the group consisting of hydrogen and C₁₋₆ alkyl,

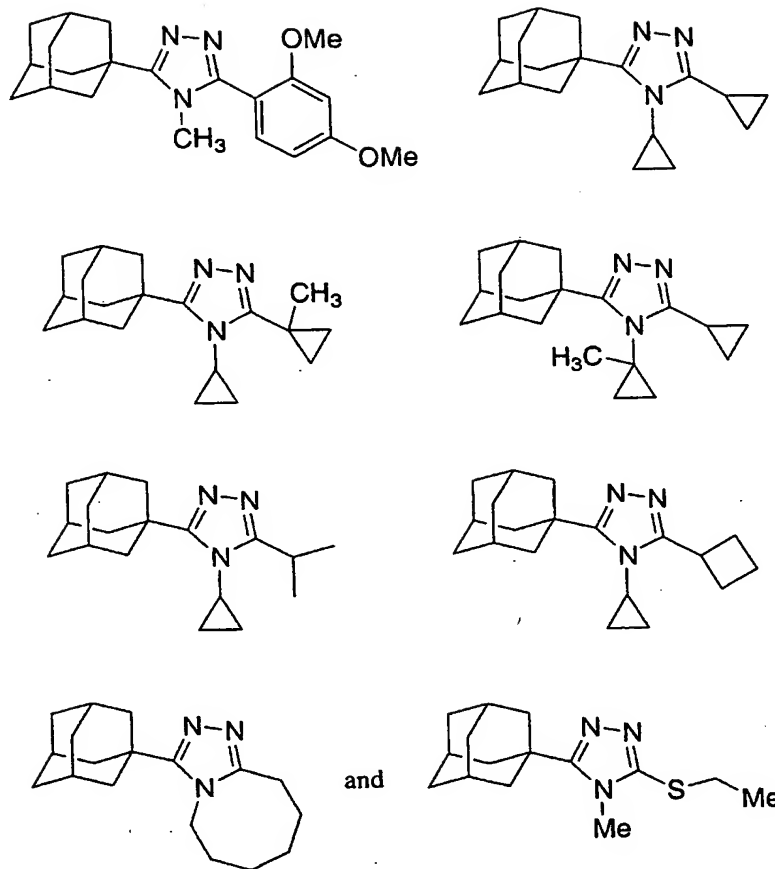
unsubstituted or substituted with one to six substituents independently selected from zero to five fluorines and zero to one phenyl, said phenyl being unsubstituted or substituted with one to three substituents independently selected from halogen, CH_3 , CF_3 , OCH_3 , and OCF_3 ;

20

wherein R^4 is unsubstituted or substituted with one to five R^c substituents, wherein each R^c is independently selected from halogen, OH, OCH_3 , OCF_3 , C₁₋₆ alkyl,

25

C₂₋₆ alkenyl, phenyl, biphenyl, C₃₋₈ cycloalkyl, C₁₋₆ alkyloxycarbonyl, an epoxide group bridging 2 adjacent carbons, and 1,3-dioxolanyl geminally disubstituted onto one carbon of R^4 , wherein each C₁₋₆ alkyl and C₂₋₆ alkenyl is unsubstituted or substituted with one to five substituents independently selected from zero to three halogens and zero to two groups selected from phenyl, C₁₋₆ alkyloxycarbonyl, 1,3-



5 or a pharmaceutically acceptable salt or prodrug thereof.

11. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

10 12. A method for treating, controlling, or delaying the onset of non-insulin dependent diabetes mellitus in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of structural formula I, or a pharmaceutically acceptable salt thereof:

wherein said C₃₋₉ cycloalkyl and C₅₋₁₂ bicycloalkyl optionally have one to two double bonds, and said C₃₋₉ cycloalkyl, C₅₋₁₂ bicycloalkyl, and adamantyl are unsubstituted or substituted with one to six substituents independently selected from (a) zero to five halogens, CH₃, CF₃, OCH₃, and OCF₃, and (b) zero or one phenyl, said phenyl being unsubstituted or substituted with one to four groups independently selected from halogen, OCH₃, OCF₃, CH₃, and CF₃;

R³ is selected from the group consisting of
hydrogen,
C₁₋₁₀ alkyl, unsubstituted or substituted with one to six substituents independently selected from zero to five halogens and zero or one group selected from hydroxy and C₁₋₃ alkoxy, said alkoxy group being unsubstituted or substituted with one to three halogens,
C₂₋₁₀ alkenyl; unsubstituted or substituted with one to six substituents independently selected from zero to five halogens and zero or one group selected from hydroxy and C₁₋₃ alkoxy, said alkoxy group being unsubstituted or substituted with one to three halogens,
YC₃₋₉ cycloalkyl,
YC₅₋₁₂ bicycloalkyl,
Yadamantyl, and
YR;

wherein said C₃₋₉ cycloalkyl and C₅₋₁₂ bicycloalkyl optionally have one to two double bonds, and said C₃₋₉ cycloalkyl, C₅₋₁₂ bicycloalkyl, and adamantyl are unsubstituted or substituted with one to six substituents independently selected from (a) zero to five halogens, CH₃, CF₃, OCH₃, and OCF₃, and (b) zero or one phenyl, said phenyl being unsubstituted or substituted with one to four groups independently selected from halogen, OCH₃, OCF₃, CH₃, and CF₃;

R is selected from the group consisting of benzodioxolane, furan, tetrahydrofuran, thiophene, tetrahydrothiophene, dihydropyran, tetrahydropyran, pyridine, piperidine, benzofuran, dihydrobenzofuran, benzothiophene, dihydrobenzothiophene, indole, dihydroindole, indene, indane, 1,3-dioxolane, 1,3-dioxane, phenyl, and naphthyl; wherein R is unsubstituted or substituted with one to four groups independently selected from halogen, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₂₋₄

phenyl, biphenyl, and C3-8 cycloalkyl, either as R^C or as a substituent on R^C, is unsubstituted or substituted with one to three groups independently selected from halogen, CH₃, CF₃, OCH₃, and OCF₃;

- 5 wherein R⁴ optionally has a fused phenyl ring, a benzodioxinyl ring, or a dihydrobenzodioxinyl ring, said phenyl ring, benzodioxinyl ring, and dihydrobenzodioxinyl ring being unsubstituted or substituted with one to three substituents independently selected from halogen, CH₃, CF₃, OCH₃, and OCF₃; and
- 10 wherein R⁴, including said optional fused phenyl ring, benzodioxinyl ring, or dihydrobenzodioxinyl ring and including all substituents on R⁴ and said fused phenyl ring, benzodioxinyl ring, and dihydrobenzodioxinyl ring, has no more than 20 carbon atoms.
- 15 13. A method for treating, controlling, or delaying hyperglycemia in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 12 or a pharmaceutically acceptable salt thereof.
- 20 14. A method for treating, controlling, delaying or preventing obesity in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 12 or a pharmaceutically acceptable salt thereof.
- 25 15. A method for treating, controlling, or delaying insulin resistance in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 12 or a pharmaceutically acceptable salt thereof.
- 30 16. A method for treating, controlling, or delaying one or more lipid disorders selected from the group consisting of dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, and high LDL in a mammalian patient in need of such treatment which comprises administering to said patient a

- agonists and (ii) biguanides;
- (c) insulin and insulin mimetics;
- (d) sulfonylureas and other insulin secretagogues;
- (e) α -glucosidase inhibitors;
- (f) glucagon receptor antagonists;
- (g) GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists;
- (h) GIP, GIP mimetics, and GIP receptor agonists;
- (i) PACAP, PACAP mimetics, and PACAP receptor 3 agonists;
- (j) cholesterol lowering agents selected from the group consisting of
- (i) HMG-CoA reductase inhibitors, (ii) sequestrants, (iii) nicotinic alcohol, nicotinic acid and salts thereof, (iv) PPAR α agonists, (v) PPAR α / γ dual agonists, (vi) inhibitors of cholesterol absorption, (vii) acyl CoA:cholesterol acyltransferase inhibitors, and (viii) anti-oxidants;
- (k) PPAR δ agonists;
- (l) antiobesity compounds;
- (m) ileal bile acid transporter inhibitors;
- (n) anti-inflammatory agents, excluding glucocorticoids; and
- (o) protein tyrosine phosphatase-1B (PTP-1B) inhibitors.

20. A method for the treatment, control, delay, or prevention of one or more conditions selected from the group consisting of hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hypertriglyceridemia, and dyslipidemia, which method comprises administering to a mammalian patient in need of such treatment a therapeutically effective amount of a compound of Claim 12 and an HMG-CoA reductase inhibitor.

21. The method of Claim 20 wherein the HMG-CoA reductase inhibitor is a statin.

22. The method of Claim 21 wherein the statin is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, itavastatin, ZD-4522 and rivastatin.

- (o) protein tyrosine phosphatase-1B (PTP-1B) inhibitors; and
(3) a pharmaceutically acceptable carrier.

27. The method of Claim 22 further comprising administering a
5 cholesterol absorption inhibitor.

28. The method of Claim 27 wherein the cholesterol absorption
inhibitor is ezetimibe.

10 29. A method of treating diabetes in a mammal in need thereof
comprising administering to the mammal a therapeutically effective amount of a
compound of Claim 12 in combination with the PPAR α / γ dual agonist KRP-297.